CYSTIC FIBROSIS IN CHILDREN AND ADOLESCENTS IN THE WESTERN CAPE:

EPIDEMIOLOGICAL AND CLINICAL ASPECTS

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ABBREVIATIONS USED THROUGHOUT THE THESIS

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
DNA	Deoxyribonucleic acid
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GSH	Groote Schuur Hospital
HIV	Human immunodeficiency virus
MI	Meconium ileus
PEG	Percutaneous endoscopic gastrostomy
PERT	Pancreatic enzyme replacement therapy
PI	Pancreatic insufficiency
PS	Pancreatic sufficiency
RCCH	Red Cross War Memorial Children's Hospital
SA	South Africa
SD	Standard deviation
TB	Tuberculosis
TBH	Tygerberg Hospital
UK	United Kingdom of Great Britain and Northern Ireland
USA	United States of America

SUMMARY

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations on chromosome 7 in the gene for the CFTR protein. This gene encodes for a chloride channel on the apical surface of certain epithelial cells. The clinical manifestations of CF largely arise out of the resultant defect in water and electrolyte secretions in exocrine glands and epithelia such as are found in the pancreas, respiratory, gastrointestinal and genital tracts and sweat glands.

First delineated as a clinical entity in the mid-20th century, CF was shown to be identifiable through the demonstration of elevated electrolyte levels in sweat – the sweat test. After many false starts, the underlying genetic defect was identified in the 1980s, culminating in the identification of the defective gene in 1989. This opened up possibilities of more accurate diagnosis and targeted treatments.

Treatment of CF with pancreatic enzyme replacement therapy and antibiotics in the 1950s proved successful in controlling some of the severe and often fatal aspects of the disease. Further refinements to nutritional and antimicrobial therapies in the 1970s and 1980s produced rapid increases in longevity in many patients with CF.

In SA, CF has been identified since the 1950s. Clinical and research activities developed in the 1980s, mainly focused on the epidemiological and genetic aspects. Two clinical studies described features in children in Cape Town and adults in Johannesburg.

My own clinical involvement in the RCCH's CF Service in Cape Town since 1992 led to the research activities that make up the bulk of this thesis.

The thesis describes a number of aspects of CF as it affects patients in SA. The **study population** (described in Chapter 2) for most of the projects consists of 181 CF patients born between October 1974 and September 2003 who were identified by a combination of clinical features, positive sweat or genetic tests and/or *post mortem* findings. All were resident in the Western Cape province and received at least part of

their health care at the RCCH. One hundred and sixty (88%) were born in the province and 21 settled in the province from elsewhere.

Cape Town is unique in SA for its population demographics and the CF patients reflect this. CF has mainly been identified in coloured and white patients. Four black cases have been diagnosed. Compared with the CF population as described in the early 1980s, the CF population in the 21st century is larger (100 versus 64), older and there is a greater proportion of coloured patients. Nearly 3 in every 4 patients live in Cape Town.

The **Epidemiology** of CF in SA is described from a population perspective ('Classical Epidemiology') and a molecular genetic perspective ('Molecular Epidemiology') in Chapter 3. Owing to uncertainties surrounding both denominators and the numerators in the only study to describe the epidemiology of CF in this region, advantage was taken of the greater time period that has elapsed to further study this aspect of CF in the Western Cape. While I was cognisant of the issues surrounding 'racial' classification in SA, I took a scientific but pragmatic approach to studying the differing epidemiologiy of CF in the 'population groups' that make up the Western Cape province's unique demographics. From the perspective of disease-causing genetic mutations, the coloured and white populations differ. Using the CF study population and birth data from the 1996 census, the incidence of CF was found to be 1 in 3 003 live births for the white population (compared with the previous figure of 1 in 2 027 live births) and 1 in 10 273 live births for the coloured population (compared with the previous figure of 1 in 12 305 live births). The incidence figure for the white population approximates that for the parts of Europe that have had the most migrants to SA. The prevalence rates per 100 000 in the population for 1996 were 53 and 28 for the white and coloured groups respectively. There is evidence that there is still under-ascertainment of coloured CF cases in non-metropolitan areas of the province.

The molecular epidemiology of CF in the white and coloured population of SA has been well described. Two CFTR mutations, ΔF508 and 3120+1G→A, are responsible for most of the CF disease in SA. The former makes up 75% of mutation in the white population and 50% in the coloured population. The latter is the second

most common mutation in the coloured population and is the single commonest mutation in the black population both in SA and in the USA.

Advantage was taken of a greater number of tested coloured patients in the local population than in any studies so far published.. In fact the published figure of 50% ΔF508 remains robust.

Combining the figures for common mutations and the new incidence figures one finds a changed set of figures for the reproductive risk predictions required for genetic counseling in the white and coloured populations.

Despite the published frequency of the 3120+1G A mutation in healthy black Africans in SA, few cases of CF have been seen. Five case reports illustrating the changing perspective on CF in black patients are described in Chapter 3. A number of theories based on possible differences in phenotype, modifying genes and health services are raised to explain the apparent under-representation of black African CF cases in SA.

Clinical aspects of CF are presented in Chapter 4. In the Western Cape province CF presented much as it does in the rest of the world. The only exception was a greater incidence of the anaemia-oedema complex in the coloured population, a possible consequence of socio-economic conditions in this region. Median age at diagnosis (no newborn screening took place) was 6 months (14,5 months if patients with MI or an older sibling were excluded). This was relatively late compared with Western norms. No improvement in age to diagnosis over the 29 years could be demonstrated.

Complications of CF were divided into those that are caused directly by the CFTR mutations, those that are secondary to these changes and those induced by therapy. PI affected 95% of patients, a relatively high figure. A full spectrum of complications of CF has been seen over the 29 years. Apart from the ubiquitous PI and lung disease, 117 of the 181 patients had at least one other complication of CF.

Chapter 5 describes the surgical experience of the CF population over 29 years. In the first 20 years 154 operations were done on 57 of 111 patients, 30% of whom had an

operation related to CF. MI dominated the major surgery. Three lobectomies were done. Outcomes were generally good and surgical and anaesthetic misadventure were minor and few (9,2% and 11,4% respectively). An update covering recent years reveals changes to practice: more operations for gastro-oesophageal reflux and the advent of percutaneously inserted gastrostomies for nocturnal calorie supplementation. Case histories of three unusual surgical presentations are described.

Attention to nutrition is a central part of CF care. Chapter 6 presents a description of nutritional indices in this CF population in two cross-sectional studies. Median percentage weight for height was 93 (interquartile range 84-101). Sixty eight percent of patients consumed less than the recommended daily intake of energy. There was an improvement in mean weight for height in the decade between 1986 and 1996.

Lung disease was difficult to study in a small population such as this. In Chapter 7 it is demonstrated that the bacteriology of CF in this region has mirrored that elsewhere with *Staphylococcus aureus* infection occurring earlier (median age 118 months) than *Pseudomonas aeruginosa* infection (median age 150 months). ΔF508 homozygosity but not ethnicity was associated with earlier infection with *P aeruginosa*.

The Cystic Fibrosis Service is described in Chapter 8. Transition to adult-oriented care has been actively worked on. In our study, concerns around the move to Groote Schuur Hospital and the independence of young people with CF were shown to be significant. A letter to the editor of *Pediatrics* demonstrates that the management of end-of-life care in our service differs from that in the USA.

Finally, the prognosis of CF in this region is the subject of Chapter 9. A 20 year study showed a median survival of about 18 years with coloured patients doing worse than white patients. A later longer study shows survival to be improving, at least for white children. Deaths in infancy still occur in the 21st century but prognosis in this region seems to be better than in other resource-poor countries.

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CHAPTER 1

INTRODUCTION

Since the delineation of its classic form by Fanconi[1], Andersen[2] and Farber[3], "cystic fibrosis of the pancreas" or "mucoviscidosis" (hereinafter, "CF") has been a source of great clinical and scientific interest. Clinicians have been fascinated by the ever-expanding spectrum of clinical problems associated with the disease. They have been heartened by their ability to extend the lives of their CF patients. Scientists, having conquered the molecular basis of CF, are still challenged to explain the exact mechanisms underlying its manifestations. Fifteen years after the identification of the cystic fibrosis transmembrane regulator (CFTR) and its associated gene, physiologists still cannot satisfactorily explain how the defect in salt and water transport caused by mutations in the gene for CFTR leads to viscid secretions in exocrine glands. This is especially the case in the lung, damage to which is the chief cause of the premature mortality associated with CF.

Cystic fibrosis as a genetic disease

CF is caused by mutations in the CFTR gene which is found on the long arm of chromosome 7. It is an autosomal recessive condition requiring that the patient receive one CFTR gene mutation from each biological parent. To date over 1000 disease-causing mutations of the CFTR gene have been described. Only a few are common; some are population-specific; most are rare, even occurring in only one family. While gene-specific clinical traits are not found with most CFTR mutations, some mutations have been associated with clinical variables such as severity of disease, organ-specific manifestations or responsiveness to specific therapies.

Thus although CF is a single gene disorder, exactly which CFTR gene mutations an individual has inherited may influence the disease's clinical form.

Cystic Fibrosis as a clinical entity

In essence CF is a disease that affects the epithelia of exocrine glands and hollow organs. Owing to a defect in the balance of water and electrolyte transport, viscid secretions are produced. These secretions are unable to move normally through the ducts and organs. This has different effects in different organ systems.

In the **pancreas**, the secretions carry digestive enzymes. When the enzymes are not satisfactorily excreted and transported to the duodenum, they digest the pancreas itself. In about 90% of CF cases, there is eventually insufficient residual pancreatic tissue to allow normal digestion of food. Untreated this leads to steatorrhoea and growth failure with multiple nutritional deficiencies. Eventually even the endocrine cells contained within the pancreas are destroyed leading to problems with glucose tolerance and overt diabetes mellitus.

In the **lung**, thick secretions lead to poor ciliary escalator function, retention of secretions and reduced clearance of pathogens. There is thus a propensity to airway obstruction, atelectasis and infection that in time leads to the destruction of lung tissue. These lung manifestations are almost universal among patients with CF.

In the **upper respiratory tract**, as with the lung, poor ciliary transport leads to inadequate clearance of secretions and increased incidence of infection, particularly sinusitis. Mucosal hypertrophy in the sinuses and polyp formation in the nose are frequent consequences.

In the **liver**, bile flow is compromised by the salt and water imbalance, leading to stasis and bile duct obstruction. The consequence of this is focal biliary cirrhosis which leads to liver cirrhosis and portal hypertension in 10-15% of CF patients.

In the **sweat glands,** salt and water imbalance leads to excess salt loss. In infancy and in hot climates or environments this can lead to the clinical consequences of salt deficiency

(failure to thrive, hypochloraemic metabolic alkalosis and heat prostration). This defect also provides the basis for the best diagnostic test for CF, the "sweat test".

In the **male genital tract**, seminal secretions are of such limited volume that the vas deferens does not form in 99% of male fetuses. The consequence of this is infertility. Females with CF are also relatively infertile owing to thick cervical mucus.

Through mechanisms not fully understood but which include secretions from mucous glands, the contents of the **intestine** may obstruct its lumen leading to meconium ileus (MI) in 10-15% of CF fetuses, and, in some older CF patients, to the distal intestinal obstruction syndrome (DIOS).

Thus CF is a multisystem disease. It is evident from the preceding discussion that how CF affects an individual patient is an amalgam of his or her genetic make-up, the range of organs involved and how severely those organs are affected. On top of this, it must be noted that the disease's course is also affected by environmental factors such as exposure to respiratory pathogens and pollutants, by parental coping styles and socio-economic factors, particularly poverty.

Milestones in the understanding and treatment of CF

The names of the Swiss paediatrician Guido Fanconi and American pathologist Dorothy Andersen are inextricably linked with the emergence of CF from the complex of conditions associated with steatorrhoea, severe failure to thrive and death in infancy and early childhood. Features of the disease such as MI and its inherited nature had been described early in the 20th century but, in the 1930s, these two workers delineated the essential features of CF and established it as a clinical entity.

In 1935 Fanconi noted the connection between "zysticher pankreasfibromatose" (cystic fibrosis of the pancreas) and "bronchiektasien" (bronchiectasis).[1] In 1938 Andersen published a paper in which 22 cases of "celiac disease" in whom pancreatic changes were identified at *post mortem* were described.[2] In her article she included another 27 cases

from the literature, including those of Fanconi. Her paper meticulously described the association of "cystic fibrosis of the pancreas" with MI and its complications, severe nutritional impairment and chronic respiratory disease characterised by plugging of the bronchial lumen by "tenaceous (sic), greenish gray (sic) mucopurulent material", abscesses and dilated bronchi. The familial nature of the disease was also noted in this classic report.

Interestingly the common pathogenesis of the pancreatic and pulmonary lesions was not postulated in either the article or discussion following the paper's first presentation on May 5, 1938. Andersen's suggestion, repeated in a later paper in which the role of *Staphylococcus aureus* in the lung disease was noted,[4 5] was that Vitamin A deficiency might have led to the bronchiectasis. In articles in 1944[3] and 1945,[6] Farber, who also remarked on the frequent association of *S aureus* with the lung disease, suggested that the feature common to both pancreas and lung was inspissation of secretions. In an article published a year later, Andersen was dismissive of this idea,[5] still believing that nutritional deficiencies, especially that of Vitamin A, led to the lung disease. Farber speculated that a problem with nervous control of mucous secretion caused the multi-organ pathological changes.[6] He coined the term "mucoviscidosis" which survives today as the name for CF in Romance languages such as French. A number of other authors confirmed this characteristic finding and CF was thus thought to be exclusively a disease of mucus-producing exocrine glands.

Bodian in 1952 established unequivocally that CF was an inherited condition with a Mendelian autosomal recessive pattern[7] (though some doubters remained right up till the time the gene was cloned).

That CF was due to a more broadly-based defect than simply that of viscid secretions came to light in 1953 when Paul di Sant'Agnese (who had previously worked with Andersen) and colleagues in New York, USA demonstrated the abnormality in sweat electrolyte concentration now known to be a cardinal, indeed diagnostic, feature of CF.[8] It was Gibson and Cooke who, six years later and at di Sant'Agnese's suggestion,

described the method of measuring sweat electrolyte concentration using pilocarpine iontophoresis, providing the only definitive *ante mortem* diagnostic test for CF until the CFTR era.[9]

By this time one of the pioneers of CF management, Dr Harry Shwachman in Boston, USA was leading the field in improving the lives of children with CF.[10] Pancreatic extracts were used to overcome the effects of pancreatic insufficiency. The antibiotic revolution was also in full swing allowing paediatricians such as Dr Shwachman to modify the effects of bacterial infection in the lung. He was able to report a rapid improvement in survival from a norm of death before two years of age in the 1930s and 1940s to death under two being a rarity by the mid-1970s.[11] He also made plain that CF is a disease of varying severity, introducing a score (which became known as the Shwachman score) by which the efficacy of new therapies might be measured.[10]

Through the 1960s and 1970s continuing efforts were made to understand the causation of CF with a myriad of potential explanations and clues being found and then discarded. "Factors" that affected ciliary function or mucus secretion, hyperpermeable mucus, disorders of calcium secretion - all were to be found in this melting pot of ideas. An advance came when Michael Knowles and colleagues demonstrated abnormal potential difference across respiratory epithelia.[12] In 1982-3 an unequivocal lead was found when Paul Quinton, himself a CF sufferer, demonstrated a defect in chloride ion resorption in the sweat glands (his own).[13] This defect was then demonstrated in other epithelia.

Simultaneously in the early 1980s, genetic studies of affected siblings and their parents showed that the CF gene was on the long arm of chromosome 7 and in a very short space of time (a reflection of the speed of the general increase in molecular genetic knowledge at that time) scientists in Toronto and Michigan had identified, cloned and named the causative gene and its protein product, CFTR.[14 15] CFTR was found to be a chloride ion channel, thus linking the physiology of CF directly to the molecular biology of CF. The world of CF had changed - vistas of new knowledge and hopes of new therapies opened up.

On a therapeutic level from the 1960s to the 1980s progress was continuing to be made, though slowly. A major conceptual change occurred in the early 1980s when it was shown by the Toronto CF Clinic that increased fat intake, introduced there in 1970, improved nutritional outcomes without unpleasant symptoms.[16] Up till this time low fat diets that decreased the steatorrhoea were the norm. The introduction of products containing microspheres of enteric-coated pancreatic enzymes radically reduced fat malabsorption. These two developments meant a much better nutritional state could be expected for CF patients, with an associated improvement in prognosis. The advent of fibrosing colonopathy and its relationship with big doses of high lipase pancreatic enzyme supplements in the 1990s led physicians to use the products more carefully.[17]

Regarding lung disease, inhaled antibiotics, although introduced in the 1950s, were only formally evaluated in the UK in the early 1980s[18] and later elsewhere.[19 20] They were shown to help with the control of *Pseudomonas aeruginosa* infections. It was also shown that permanent infection of the lungs by this organism could be postponed by early aggressive antibiotic use.[21]

The major role of the immune system in the pathophysiology of CF lung disease was detailed in the 1990s.[22] The full benefit of this knowledge has yet to be felt at a clinical level with oral steroids having significant side effects[23] and non-steroidal anti-inflammatory drugs and inhaled anti-proteases being difficult to use.[24] Heart lung transplant was introduced in 1984 and is now established practice for late-stage CF in many countries.[25]

By the mid-1990s median survival had increased to more than 30 years in many countries[26] and competition between centres to improve outcomes became intense.

The advent of the third millennium finds CF scientists hard at work pushing back the frontiers of knowledge. As they work with CFTR at a physiological and molecular genetic level, their clinical colleagues find themselves somewhat marking time,

continuing to promote "established CF therapy" (attention to nutrition, antibiotics, physiotherapy, pancreatic enzyme replacement) while awaiting the fruits of this science.

Cystic fibrosis in South Africa

There has not been a shortage of interest in CF among clinicians and scientists in southern Africa. A lone report in 1958 from a clinician in Johannesburg shows that CF was being sought even then. Catzel, who had worked with Shwachman, investigated 230 children, mostly 'Bantu-speakers', with Shwachman's new screening test: the agar plate 'Finger-print sweat test'.[27] He was clearly disappointed not to find any black African CF patients and he thought very highly of the discriminatory power of Shwachman's test. Though compared to the USA and Europe, other South African authors were slow off the mark, by the 1980s and 1990s there was a steady flow of reports on many aspects of the disease as experienced in this part of the world.

First reports of CF in South Africa (SA) were, ironically, of black African children. These cases represented something unusual, suggesting that CF was being seen by clinicians among populations of European stock – Catzel would have been an example of such a clinician. That CF was relatively common amongst southern Africa's European populations was brought to local and international attention by Super in the then South West Africa (SWA) who suggested that the incidence of CF in that country was 1:622 white newborns.[28] Later, using a questionnaire survey and MI data, he revised these figures to 1:635 to 1:1192 - the highest incidence in the world, it appeared.[29] In the same study he suggested that the minimum incidence in SA was between 1:5175 and 1:6534 white newborns. He noted that amongst people of European stock, Afrikaners had a higher incidence than Britons. Botha and Beighton in SA also noted that CF was a significantly common condition amongst Afrikaners.[30] Super also noted the presence of CF in a few coloured and black African South Africans.[28]

Super devoted much of his thesis on CF, completed in 1978, to an exploration of putative reasons for the high incidence of the disease amongst SWA's Afrikaners.[31] These varied

from heterozygote immunity to malaria to increased mutation rates because of elderly fathers. He was unable to prove any of these theories.

On a **clinical** level Super's thesis examined a small number of CF patients, illustrating the variety of clinical courses associated with the disease.[31] Most of the children he described died in infancy and early childhood. In contrast, in the early 1980s clinicians in Johannesburg were able to describe a group of 33 adolescents and adults with CF (all of whom were of European origin), paralleling articles from a decade earlier in Europe.[32] The Cape Town CF Clinic outlined their experience in an article in 1988.[33]

The Cape Town paper also shed new light on the **epidemiology** of CF: the incidence was more like that of Europe than Super[34] had suggested (incidence among whites was 1:2027), and it was not uncommon among the coloured population of the western Cape Province (Chapter 3 discusses epidemiology in detail).[33] That CF was rare among SA's black African population seemed self-evident through the lack of clinical cases. Super described one case in his thesis but was not convinced that she really had the disease,[34] and noted a few in his 1978 paper.[28]

During the 1980s, social scientists in Cape Town took an interest in the effect of CF on families. De Wet, working under the guidance of Prof. S Cywes, the head of Paediatric Surgery at the Red Cross Children's Hospital (RCCH), explored parental reaction to the diagnostic process in CF.[35-37] Henley, working with Dr I Hill, produced a doctoral thesis and two papers which examined CF families' understanding of CF and its treatment.[38 39]

In his 1975 article and 1978 thesis, Super expressed enthusiasm for bringing together southern African scientists, clinicians and CF families. CF associations developed in SA's provinces, their aims being the promotion of CF awareness and support of families facing CF. In 1989 the provincial groups came together and formed an umbrella body, the South African Cystic Fibrosis Association (SACFA). This association funded a Medical and Scientific Advisory Committee (MSAC) on which sat senior clinicians and scientists with experience in CF matters. This body, established in 1991, has overseen

the introduction of new tests and therapies for CF in the country and has arranged regular symposia, keeping workers in CF abreast of scientific and medical developments. It has also taken the needs of CF patients to the highest offices in the Department of Health and represented SA's CF scientists internationally.

The advent of reasonably accurate **prenatal diagnosis** of CF for affected families in the early 1980s was enthusiastically greeted in SA. Nelson and colleagues from Cape Town reported their findings[40] less than two years after the first report of the utility of measuring levels of a specific alkaline phosphatase in the amniotic fluid had been reported in a scientific letter by Brock and colleagues in Edinburgh.[41]

Within three years however DNA-based prenatal diagnosis using polymorphic markers was introduced in Johannesburg and Cape Town for affected families. The utility of the two forms of prenatal testing in SA were compared in an collaborative article from the two centres.[42] Ironically, by the time this article was published in 1991, the CFTR gene had been cloned and new and even more exciting and widely applicable methods of prenatal diagnosis became available to South Africans in the form of CFTR mutation analysis.[15]

Soon after the appearance of the article from Cape Town on the epidemiology of CF, the CF gene was cloned in North America. With this major advance, new avenues of epidemiological opened to SA's scientists as carriers of common mutations could now be identified. The genetic basis of CF in SA could now be explored.

Through the 1990s to the present day many articles appeared as South African scientists and clinicians sought to define the **genetic** characteristics of CF as it occurs in the region.[43-48] Most interesting among these was the discovery that, not only were CFTR gene mutations and CF patients to be found among SA's black chiefdoms, they appeared to be a by no means rare phenomenon![49 50]

The author's involvement in cystic fibrosis

I joined the RCCH CF Clinic in February 1992 when I began work as a specialist at the hospital. I had met children with CF in the hospital wards during my paediatric training. I had not realised how complex and wide was the range of problems associated with the disease. This soon dawned on my callow consciousness as I met the children and their families in the Clinic.

In an attempt to understand the disease better I studied its **surgical complications** under the guidance of the senior consultants at the Clinic (Prof. M Bowie and Dr J Ireland). This work, published later in the *South African Journal of Surgery*,[51] also resulted in an updated database of patients who had been diagnosed as having CF at the hospital or who received follow-up at the Clinic. This database I have maintained to the present.

The surgical study had covered 20 years of experience with CF at the hospital. By mining further into the data I was able to explore the **prognosis** of CF in the Western Cape province and the factors affecting outcome. The paper arising from this study was published in 1996.[52] The circumstances of these CF **death**s were examined in response to an article published in *Pediatrics* by a CF Clinic in the USA.[53] I responded in letter form giving contrasting data from Cape Town.[54]

By now the bit was firmly between my teeth and, while preparing and publishing a book of **nutrition** in CF for South African patients and their families to use, I initiated studies of nutritional aspects of CF. This led to a B. Sc. (Hons) dissertation for my co-worker, Romy Saitowitz who studied calcium intake and metabolism, and two papers published in 1999 and 2000.[55 56]

The psychosocial aspects of chronic illness have always interested me and, in 1996, with the help of Dr Lesley Henley, a study of the process of **transition** between RCCH CF Clinic and Groote Schuur Hospital's (GSH) Respiratory Clinic was conducted. The paper this work produced was published in 1999.[57]

In 1993, for the first time in Cape Town (apparently – see p67), a Xhosa child was found to have CF. We had also noted an increase in the proportion of coloured CF patients seen at the Clinic. These two changes led to a collaboration with Prof. M Ramsay and her workers in the Department of **Genetics** at the South African Institute for Medical Research at the University of the Witwatersrand in Johannesburg.[48] This resulted in our database containing the genotype details of a 'racial' mix that is unique internationally and in SA. The large numbers of new coloured CF patients identified in the 1990s also led us to re-examine the **epidemiology** of CF in the Western Cape province: Hill and colleagues' paper of 1988 needed review and updating (see Chapter 3).

The late 1990s and the start of this century have brought an increase in therapeutic options for lung infections in CF. This has prompted a review of the **bacteriology** of the lung disease in CF, particularly the time to first infection with the common pathogens, *S aureus* and *P aeruginosa* (see Chapter 7).

This thesis takes in all these studies. Other studies conducted through the clinic in which the initiation and the bulk of the work have been done by colleagues (lung function by Dr H Zar; adolescent body image by Dr L Carew), though referred to, do not form part of this work.

The scope and aim of the thesis

The thesis brings together in one document all my studies over the past 10 years. In some the data are given as previously published. Others have been updated and some contain data that has not been published before. The aim is to give as comprehensive a view as possible of how CF has affected children, adolescents and young adults in the Western Cape province over the past 30 years.

The structure of the thesis

Each chapter explores one aspect of CF and may encompass one or more studies. The study population and database are described in Chapter 2. Thereafter each chapter contains its own Literature review, Methods, Results and Discussion sections.

CHAPTER 2

THE STUDY POPULATION

All the studies reported in this thesis were undertaken on children and adolescents who had been diagnosed as having CF. What constitutes clinical CF has become a matter of debate in clinical and research circles since the identification of the molecular basis of the disease in 1989.[14 15] Thus, before the criteria for inclusion of patients in the study populations are described, current issues and recommendations surrounding the diagnosis of CF will be presented.

What is cystic fibrosis?

Before the molecular basis of CF was elucidated, it was relatively simple to define CF by its clinical features and positive sweat tests. Although it required fussy attention to detail, the Gibson-Cooke method of performing a sweat test using pilocarpine electrophoresis proved very useful in identifying typical CF.[9] True, there was a list of conditions that produced false positive results but few of these had more than one clinical feature in common with CF.[58] It was also possible to enhance the utility of the test in cases with borderline sweat electrolyte levels by testing the response to fludrocortisone, a potent mineralocorticoid.[59] Unchanged electrolyte levels after two doses was characteristic of CF; a decline made the diagnosis of CF much less likely.

The identification of CFTR has made it possible to find gene mutations in persons with very mild symptoms (e.g. sinusitis, absent vas deferens) and no pancreatic or lung disease. Often the sweat test is normal in such cases.[60] Do these persons have CF? Conversely, patients have been described with many clinical features of CF who have no CFTR mutation.[61] Do these persons have CF? The S1455X mutation causes elevated sweat electrolyte levels mediated through CFTR but no other manifestations of CF?[62] Do persons with this mutation have CF?

To attempt to bring uniformity to nomenclature in clinical CF, international organisations have, in recent years, attempted to define what constitutes a diagnosis of CF. The Cystic Fibrosis Foundation Consensus Panel (CFFCP) in the United States of America published their statement in 1998.[63] Their recommendations required

A) i) At least one of 4 phenotypic features, or
ii) a history of CF in a sibling, or
iii) a positive newborn screening test.

And

B) evidence of CFTR abnormality (i.e. abnormal sweat tests; CFTR mutations on both 7th chromosomes; or *in vivo* demonstration of characteristic abnormalities in ion transport across nasal epithelium [This latter test is not available in South Africa].)

Full details of the interpretation of these tests were given in the CFFCP statement. The report emphasises the priority of the sweat test in making a diagnosis of CF especially where mutation analysis is uninformative. The continuing priority of the sweat test was reinforced by Wallis (incidentally, a former member of the RCCH CF team) in an annotation from the United Kingdom (UK).[64]

The CFFCP classification was challenged by Bush and Wallis who were concerned at the potential labelling of genetic abnormality or subclinical organ damage as CF "disease". For example, the fulfilling of condition A through having a sibling with CF would label a child as having CF if he or she had CF mutations even if the child was asymptomatic and had no evidence of airway or pancreatic disease. They suggested categories of *pre-clinical* and *sub-clinical* CF be created. Children in such categories could be monitored for the development of clinical disease but not treated as having it.[65]

In response to debates such as these, the World Health Organisation (WHO) convened a panel of experts in 2000 to classify the disease for epidemiological purposes. The classification which uses the overall term "Cystic Fibrosis and Related Disorders" and which depends on a mixture of phenotypic and genotypic features appears in Table 2.1.[66]

TABLE 2.1 CYSTIC FIBROSIS AND RELATED DISORDERS
Classical CF pancreatic-insufficient (PI)
Classical CF pancreatic-sufficient (PS)
Atypical CF
CF other specified
CF not otherwise specified
Isolated obstructive azoospermia*
Chronic pancreatitis*
Allergic bronchopulmonary aspergillosis (ABPA)*
Disseminated bronchiectasis*
Diffuse panbronchiolitis*
Sclerosing cholangitis*
Neonatal hypertrypsinogenaemia

*At least one CFTR mutation identified

That this classification will need revision as knowledge and understanding of these conditions expands is acknowledged in the WHO report.

Identification of cystic fibrosis in Cape Town

The studies to be described in this thesis cover years before and after the advent of CFTR mutation analysis. Prior to 1989 the sweat test, performed according to the Gibson-Cooke method and repeated if positive, was used to confirm a diagnosis of CF. Both the sweat test and mutation analysis have been used as diagnostic tests since 1989. The CF Clinic at the RCCH has always carried a few children in whom the diagnosis of CF is not clear owing to atypical or mild clinical features and/or equivocal or variable sweat electrolyte results.

The compilation of the Study Population

There have been two phases in this process. The first was retrospective:

In 1993, when I began my first CF-related research, I compiled a database of patients through exploring the RCCH CF Clinic records. All outpatient notes had been recorded in duplicate and the notes of patients who had died or been transferred had been kept in the same filing cabinet as current patients' records. From this source a list of past and current patients was compiled.

Further patients were identified from copies of surgical. summaries arranged by diagnosis in the Department of Paediatric Surgery. Summaries under the headings Meconium ileus, Mucoviscidosis and Cystic Fibrosis were examined and patients entered into the database if they fitted the criteria for CF.

Another source of data was the raw data sheets from Hill and colleagues' epidemiological and clinical study published in 1988. Hospital folders of patients not already entered into my database were studied for proof of the diagnosis of CF. This source yielded a few patients who had died in hospital before being seen in the CF outpatient clinic. Two or three more patients were identified through examining ward-based summaries of admissions in the early 1990s.

This process identified 130 CF patients for whom 128 folders could be accessed.

The second phase of the compilation was prospective:

Since the compilation of the retrospective database, all new CF patients who have been seen at the hospital and were resident in the Western Cape province before September 2003 have been added to the database that forms the basis of this work. As with the first phase this includes patients referred to the CF Clinic, patients identified in hospital and patients identified *post mortem*.

Every attempt has been made to identify all children and adolescents diagnosed as having CF in the Western Cape region up to September 2003. This has been both to offer such young people the benefits of receiving care at a specialised CF centre and in order to arrive at accurate epidemiological and prognostic figures for the region.

This second phase has added 80 more patients to the list all of whose folders have been available for scrutiny. The total of potential CF patients for study was thus 208 (i.e. 128 retrospective and 80 prospective).

Almost all studies reported in this thesis aimed to describe patterns of CF-related disease and its health care for children and adolescents who live or lived in the Western Cape province region. The aims of all the clinical studies required that the

subjects had received at least some of their health care at the RCCH. They also required that sufficient clinical detail be available. Thus, given the thrust of this thesis, criteria that included diagnostic, geographical and health care stipulations were needed to define the study population for almost all studies (for the exceptions to this p18). These criteria are shown in Box 2.1.

Within this definition, individual studies had other specific inclusion and exclusion criteria depending on their objectives. These are detailed in the individual reports in later chapters.

By this definition, the Study Population of children and adolescents with CF who were resident in the Western Cape province and had received some of their CF care at the RCCH consisted of 181 subjects. The full anonymised patient set with diagnostic and demographic details is given in Appendix A.

BOX 2.1

DEFINITION OF CASES OF CYSTIC FIBROSIS FOR STUDY

Inclusion criteria:

A) **Proven cystic fibrosis**

One or more of the following criteria:

1) Two positive sweat tests carried out by pilocarpine iontophoresis at a reputable centre (mostly RCCH); and/or

2) Two CFTR mutations known to cause CF; and/or

3) *Post mortem* features for which CF was the most likely diagnosis

AND

clinical features compatible with a diagnosis of CF.

B) Resident in the regions of the former Cape Province incorporated into the Western Cape province and receiving health care for CF in the province

C) Unless diagnosed *post mortem*, seen at least once at the RCCH for CF-related disease.

D) Born after September 1974*

* For the purposes of all studies except one (Study 5.1 which used patients seen at the hospital from January 1972), clinical details were often not complete for patients born before this date.

There are three studies reported in this thesis that, for reasons related to their scientific objectives, use patients beyond the date of birth, geographical and RCCH care stipulations in the definition.

1) Surgical complications of CF (Study 5.1 Chapter 5)
   --- patients are included from 1972
2) Epidemiology of CF (Study 3.1 Chapter 3)
   --- all known CF patients in the Western Cape province
3) Transition to adult-oriented care in CF (Study 8.1 Chapter 8)
   --- patients attending GSH at the time of the study were included

These study populations are defined in more detail in these chapters.

How successful is this attempt to identify all children and adolescents with proven CF likely to have been? The RCCH has been and remains a referral centre for children for the Western Cape province and, for certain highly specialised services, the rest of SA. A specialised CF Clinic was set up at the hospital in the early 1970s under the auspices of the Gastroenterology Service. Until the late 1980s this Clinic was the only specialised CF service in the western part of the then Cape Province and remains the only such service for children and young adolescents. Until 1989 all CF patients were seen at this Clinic; since then adolescents have been transferred to GSH at about 18 years of age. Physicians throughout the region (including other academic centres) were encouraged to refer patients to the RCCH for confirmation of the diagnosis and for ongoing care. The Clinic co-operated with the Genetic Department at Tygerberg Hospital (TBH) in managing the genetic aspects of the disease including antenatal testing for CF.

There has also been a close working relationship between the CF Service at the RCCH, the Cape CF Association (a lay organisation promoting the welfare of persons with CF) and the Departments of Molecular Genetics at the Universities of Stellenbosch and the Witwatersrand. This co-operation and the RCCH's reputation as a centre of excellence for CF have ensured that almost all children with CF are known to the CF Service and almost all of these have received the majority of their care at the hospital.

Within the RCCH there is close liaison between surgical departments and the medical division that includes the CF Service. Likewise laboratory staff inform the CF Clinic staff of any positive sweat test result.

For all these reasons it is very likely that the 181 patients in this CF population represent almost all children recognised as having CF in the Western Cape province in the 29 years since October 1974.

Characteristics of the Study Population

Of the 181 patients, 96 (53%) were male. One hundred and sixty (88%) were born in the province and 21 settled in the province from elsewhere. Seven left to settle elsewhere with one returning after a number of years. Contact was lost with 4 patients. Sixty one (33,7%) patients are known to have died. (The prognosis of CF in this population is discussed in detail in Chapter 9.)

The population includes one family with three siblings with CF and 14 sibling pairs with CF. One sibling pair had a mother who had CF. Two extended families included first cousins with CF (6 children in all).

Cape Town is unique in SA for its population demographics and the CF patients reflect this. That CF was not uncommon in the coloured community was shown by Hill and colleagues who reported that 30% of patients came from this community.[33] The breakdown of the current Study Population according to ethnic group is shown in Table 2.2. (For a full discussion of the use or the terms 'coloured', 'white' and 'black African', see Chapter 3 p25.)

TABLE 2.2 Cystic fibrosis population by 'ethnic group'

GROUP	NUMBER	PERCENTAGE
White	101	55,8
Coloured	76	42,0
Black African	3	1,6
Asian	1	0,6

As will be shown in Chapter 3, the genetic basis of CF is different in each of these groups. Because of the 'race'-based policies in the country for much of the study

period, there was also a significant difference in socio-economic status between the groups. Because of these differences (and possibly also because of cultural differences) the effect of 'ethnic group' on clinical and prognostic features of CF in the Western Cape province will be explored in Chapters 3 and 9. The opportunity to update knowledge of the epidemiology of CF using this larger population than the one on which current incidence, prevalence and carrier rates in white and coloured populations are based is followed through in Chapter 3.

It is interesting to compare this population with that described in the mid-1980s from the RCCH.[33] Up till then (and although it is not stated, patients may have attended the hospital from as early as 1956, the year the hospital opened) 86 CF patients resident in the western Cape Province had been seen at the hospital (20 other patients described did not reside in the province). There are now more than twice as many CF patients to learn from. At that time 30% of patients (32 patients) were from the coloured population; from 1974 onwards, 42% (76 patients) have been. Black African CF patients had not been identified at the hospital then; now three attend (five have been diagnosed but one was resident in the Eastern Cape province - see Chapter 3 p67).

It is difficult to compare the mortality of 21% by the mid 1980s and 33,7% between 1974 and the present. Length of follow up is not given by Hill and colleagues and all deaths had taken place before 10 years of age.[33] In more recent times, as shown in Chapter 9, death (at least among white patients) was unusual before that age. It is likely therefore that the higher mortality reflects longer follow up rather than worse prognosis.

The study population at the end of the compilation period (September 2003)

One hundred patients from this population of 181 were known to be alive and receiving health care in the province in September 2003. Eighty three, with an age range of 5 months to 19 years, attended the RCCH and 17 attended GSH, TBH or private practice. The oldest patient was born in 1975 (28 years old).

Of the 83 patients at RCCH, 12 were not born in the Western Cape province. Forty seven patients are white, 32 coloured, 3 black African and one Asian. Their ages are shown in Table 2.3.

Table 2.3 Ages of patients at Red Cross Children's Hospital Cystic Fibrosis Clinic

Age	Number (%)
< 1 year	5 (6)
1 – 5 years	16 (19)
5 – 10 years	25 (30)
> 10 years	37 (46)

In comparing these characteristics with the state of the clinic in the 1980s as reported by Hill and colleagues, [33] three changes stand out. Firstly the clinic has become 30% larger (83 patients versus 64 patients) despite the adults having moved to GSH from 1989. Secondly there are more older patients. Hill and colleagues reported that 67% of their clinic was under the age of 10 years. The equivalent figure in 2003 was 55% meaning that nearly half of all patients exceed this age. Both these factors have implications for how the clinic is run and what it costs to do so. If one combines this figure for patients over 10 years of age with that for adult patients attending the GSH CF service (including the 17 older survivors from this population), it is clear that there has been a sea change in the experience with CF in the Western Cape province in just under 20 years.

The third point is the changed 'ethnic' make up of the clinic. Forty three percent of patients were non-Caucasoids in 2003. Of the 71 patients used by Hill and colleagues to calculate the prevalence of CF, 21 (29,6%) were coloured and the rest were white.[33] This change has occurred despite the higher mortality of coloured CF patients which was shown in my 1996 paper on the prognosis of CF in the Western Cape province.[52] The lower socio-economic and educational status of many coloured families compared to white patients means that this change is likely to influence the amount of support the clinic needs to give to patients. It also has implications for the complexity of genetic counselling as ΔF508 homozygosity is less common in non-Caucasoid patients.

The geographic location of patients at the CF Clinic in 2003 was as follows. A large majority of patients, 61 in all (73,5%), resided in the Cape Metropole region i.e. within 40 kilometres of the RCCH. Twelve resided in the Boland/Overberg region, 7 in the West Coast/Winelands region and 5 in the Southern Cape/Karoo region.

CHAPTER 3

EPIDEMIOLOGICAL ASPECTS

OUTLINE OF CHAPTER

This chapter details both the classic and molecular epidemiology of CF in the Western Cape province. After a discussion of 'race' in South African medical literature, new epidemiological data, presented in two studies, is compared with previous Western Cape and South African literature on these subjects. Experience with CF in black patients is then presented.

Introduction

The epidemiology of a Mendelian genetic condition such as CF can be described in two linked ways. Firstly, it can be described in the classic way (Classic Epidemiology) with incidences and prevalences being given based on clinically identified cases of the condition. The condition's Mendelian inheritance minimises analysis of risk factors in its epidemiology and focuses interest on carrier rates and reproductive risk in populations with differing genetic histories.

Secondly, the major advances in molecular genetics of the last two decades make it possible to describe conditions such as CF in terms of individual mutations in the human genome (Molecular Epidemiology). Tracing the pattern of these mutations in different populations casts further light on the history of individual disease-causing genes and populations. It also informs the clinical and diagnostic aspects of the condition, leading to greater understanding of the condition's place in the health of human populations.

This chapter will present data covering both the classic and molecular epidemiological views of CF.

THE DEMOGRAPHICS OF SOUTH AFRICA AND THE WESTERN CAPE PROVINCE

South Africa (SA), the 'Rainbow Nation', is mainly populated by immigrants. Most current populations are made up of persons whose ancestors arrived in the region in the last 500 to 1000 years. South African European Caucasoids ('white') largely hail from Western Europe as a result of migration through the 17th to 20th centuries. First came the Dutch, followed soon by French and German immigrants. Later the British arrived and, in the last 100 years, immigrants from most European countries have settled in SA. While by no means mutually exclusive in their origins, the white population can largely be divided into two groups: English-speaking and Afrikaans-speaking. The 'mixed race' ('coloured') population contains a variable admixture of the inhabitants of the Cape of Good Hope at the time of European settlement (KhoiKhoi and San), European, East Asian and black African populations. The Negroid ('black African') population results from the southward extension of the Bantu expansion. The white and coloured populations contain almost all clinically identified cases of CF in SA.

The Western Cape province has three main population groups: coloured (approximately 54% of the total), Xhosa-speaking black Africans (21%) and white (20%) (Census 1996). Given the diverse origins of these three groups, a Mendelian genetic condition such as CF is likely to have a different epidemiology in each group.

The issue of 'race' in medical research in South Africa

The foregoing section has used many terms to describe the groups who live in SA and the Western Cape province. These terms have arisen in anthropological science, common custom and, more sinisterly, the social, political and legal history of SA. It is necessary in a work of medical science such as this to ensure that any terms used are appropriate to the scientific questions being asked and are non-pejorative in their usage.

'Race', in anthropology, is not a valid concept. As Cavalli-Sforza and colleagues in their comprehensive work on human population genetics point out,

> .....the concept of race has failed to obtain any consensus;
> none is likely, given the gradual variation in existence.[67]

Superficially recognisable features such as hair colour and facial structure do not reflect significant differences at a genetic level. Partition into groups on the basis of genetic analysis is by its very nature arbitrary and uncertain.

The validity of 'race' as a point of departure in medical research is also disputed. This is a corrective to a situation in which 'race' was used unthinkingly as a variable, regardless of any biological pertinence to the scientific question being pursued. This was raised in the 1980s in SA's dental literature[68] and in the 1990s in the country's medical literature.[69-71] The authors of these articles maintained that assumptions had been made regarding groups and their make up that had led to erroneous (and sometimes degrading) conclusions. As pointed out by Ellison and colleagues who had initiated a heated discussion in the pages of the *South African Medical Journal* in 1996 and 1997,[69] 'race' or 'ethnicity' in medical research have to be used with great circumspection, particularly in SA, as many of their apparent effects on health may be related more to social than biological factors. They showed that in SA, 'race' and its surrogate terms had been used indiscriminately in medical writing leading to false or inadequate conclusions regarding the effect of 'race' on medical outcomes. In response to a letter from ARP Walker (a doyen of SA's medical research) and colleagues in which, among other issues, the use of 'race' in research on single gene disorders such as Tay-Sachs disease which have high incidences in certain groups was defended,[70] Ellison and colleagues wrote

> While interethnic differences in some genetic disorders, such as sickle-cell anaemia and Tay-Sachs disease, are known to be due to ethnic differences in the frequency of those genes responsible, few genetic disorders are linked to traditional 'racial' characteristics,.....[71]

Following Ramphele who raised the pernicious use of 'race' in South African medical research in 1992,[72] Ellison and colleagues stated that, in order to avoid the potential misleading use of 'racial' terms, "[u]nambiguous and detailed definitions" of 'racial' groups should be given.[71]

On the Genetics of being called Coloured ('Race' in medical research in South Africa)

This section, with its intentionally confused title, heralds this necessary discussion on 'ethnic' classification in SA and in this thesis. It discusses two important questions that have to be answered before what follows can be evaluated for its validity:

1) Are the white and coloured populations described in this work genetically distinct?
2) How was each subject classified?

Embedded in these two questions is the issue of the use of the terms 'white' and 'coloured'. This will be dealt with when Question 2 is discussed (p28).

In the South African context, these two questions have troublesome resonances. The first is a valid scientific question whose answer caused much furore when Apartheid held sway. Every attempt was made to give the second question an anthropologically scientific and legal validity under the terms of the 1950 Population Registration Act in SA. This Apartheid-inspired Act together with the Group Areas Act of 1950 (and subsequent amendments to both) required a rigid separation of 'White' and 'Coloured' persons. When classification of persons into groups proved unworkable for the 'Coloured' group, an amendment to the Population Registration Act subdivided 'Coloureds' into seven 'distinct' groups. The pain and disruption of this classification system and its consequences have been felt and are still felt in the Western Cape province. Those classified as 'Coloured' were subject to the discriminatory laws that went with the system whose aim was to separate the 'races' from each other. Those classified as 'White' entered into a system designed, by and large, to their benefit despite Apartheid's slogan, "Separate but equal".

The present work explores a condition (CF) whose basis is entirely biological. As a single gene disorder (like Tay-Sachs disease), its presence in human populations relates to their genetic and evolutionary histories. To explore its epidemiology through the description of its appearance in different populations is, on the face of it, valid but needs clarification in the SA context where 'racial' terms have been widely used for different purposes and with different meanings.

In modern anthropological terms, the 'distance' between populations is the 'distance' between their genes. The greater the 'distance', the greater the differences in their

genetic diversity and phenotypic expression will be (and the further back in time will their common evolution be). The point at which populations are considered to be different may depend on the problem being studied.[67]

QUESTION ONE

Are the white and coloured populations of the Western Cape Province genetically distinct?

From the point of view of the study of a genetic condition such as CF, the white and coloured populations of the Western Cape Province are different. Their histories overlap, their genes overlap, but there are sufficient differences genetically for their classification into two groups when genetic disease is to be discussed. The evidence comes from studies of allotypes and of genetic disorders.

While he was not the first person to explore allotypes in SA's populations, Botha, in his 1972 study of blood groups in the Western Cape undertook by far the largest investigation into population genetics in the area up to that time.[73] Using data from blood specimens from blood donors and scholars from around the Cape Peninsula, he explored similarities and differences of a number of red blood cell antigen systems between 'White Afrikaans speakers', 'White English-speakers' and 'Cape Coloured' persons. In placing his results in the context of the histories of the groups, he attempted to calculate the size of differences and similarities in the genetic structures of the populations groups. That the differences in histories led to genetic differences between the 'White' groups and the 'Cape Coloured' group was incontrovertible, but that the immigrant groups had evidence of significant admixture of southern African and, in the case of 'Afrikaans-speaking White' group, Asian genes was also certain. Despite a declaration by the Afrikaner Studentebond in the year before Botha's publication of these results that the ancestry of the Coloured people of SA did not include 'White' genes,[74] 'race' was not an all-or-none phenomenon. The 'Cape Coloured' genetic base was KhoiKhoi (Botha used the term 'Hottentot'), European, Negroid and South and South East Asian. Botha's findings landed him in political hot water at the time with denunciations from high levels in Afrikanerdom (*ibid* p136). His findings were firmly supported by Jenkins from the University of the Witwatersrand whose parallel investigation in Johannesburg had not yet been

published.[75] The 'Coloured' population of the Reef had a greater Negroid contribution, but Jenkins' results otherwise reproduced what Botha had found.

Writing later, Nurse and Jenkins from Johannesburg stated, on the basis of their researches, that

> In South Africa a 'Coloured' (sic) is not simply someone of mixed ancestry, but someone into whose ancestry a Caucasoid element has entered.[76]

They then pointed to the unique ancestry of 'Coloured' people at the Cape where Caucasoid, KhoiKhoi, East and South Asian and, to a lesser extent, Negroid (mainly from slave imports from West and East Africa) had made genetic contributions in the last three centuries.

That the 'Cape Coloured' population is genetically distinct has had more recent confirmation from a study of GM/KM allotypes in populations from all over Africa. This study (performed by researchers not one of whom came from Africa) showed the 'Cape Coloured' to be genetically distant from Negroid, Khoisanid and Caucasoid populations while containing significant affinities with the latter two groups.[77] These results together with those from Botha and Nurse and Jenkins indicate that, in genetic terms (and answering the questioned posed above), white and coloured populations differ. [The Negroid affinities of the coloured population will be discussed when the molecular genetics of CF in this group (p58).]

Studies of monogenic disorders other than CF also give insight into the genetic distinctiveness and affinities of the coloured population. Haemoglobinopathies such as haemoglobins S and C and beta thalassaemia that are not found or are rare in white immigrant communities are not infrequently found in this population (F Desai – personal communication). Familial hypercholesterolaemia (FH), a condition whose presence in SA's Afrikaners, Jews and Indians is ascribed largely to genetic drift ('founder effect'), has been genetically investigated in coloured persons with the disease.[78] "Afrikaner" mutations in the low density lipoprotein receptor genes were found and haplotypes were identical indicating a common genetic origin. Lithuanian Jewish and Gujerati mutations were also present in coloured patients. Six of seven mutations known to be prevalent in SA accounted for 22% of FH in coloured patients.

Mirroring the situation with CF, there was a lower incidence in the coloured population than the populations from whom the mutations came, but a higher incidence than in SA black African in whom FH is rare. In another genetic example, the 677C→T mutation of the methylenetetrahydrofolate reductase gene that can lead to hyperhomocysteinaemia, a cardiovascular disease risk factor, was found in frequencies in the coloured population between those for white and black African subjects.[79]

Studies of SA's Caucasoid populations, whether English- or Afrikaans-speaking, suggest strong similarity to each other and to their north-west European forebears[76 p204-206]. Botha, exploring blood groups found the differences in admixture mentioned above, but the Caucasoids of the Cape were otherwise very similar. Indeed, the difference in admixture was questioned by Nurse and Jenkins who felt that it might reflect assimilation of coloured persons 'passing for white'.[73 p205]

QUESTION 2

How was each CF subject classified?

Though coloured and white populations may differ genetically, classification of the individual on the basis of genetic testing is not practical or adequately predictive. Not all the above studies state how subjects whose genotypes and phenotypes were examined were defined. Botha, working in the time of mandatory 'racial' classification used forms that blood donors completed.[73] Nurse and Jenkins used morphology.[76] Others do not state how classification took place. All methods were undoubtedly to some degree subjective or influenced by socio-political orthodoxy.

In the studies that follow, 'black African' subjects were those whose home language was Xhosa. Except in one case (a child of South Asian descent, see below), non-Xhosa-speaking subjects were dichotomised into 'white' or 'coloured'. Lower case initial letters are used to avoid suggesting that the categories have any basis beyond that which I have given them in this work.

Until very recently it was the practice in South African hospitals to register patients' gender and 'race' by one of eight digits on the hospital sticker, based on a form filled in by the patient or parent. '1' and '2' indicated 'White' males and females respectively; '3' and '4' indicated 'Coloured' males and females respectively. In this work, the first two categories have been called white and the latter two, coloured. The few patients diagnosed since classification at registration ceased have been classified based on a combination of features such as skin, iris and hair pigmentation and suburb of residence. The outcome of these methods of classification is that the white group will include English- and Afrikaans-speaking European and Jewish subjects. The coloured group could include Cape Malay and Khoi subjects and does include three children whose fathers were white and mothers coloured (2 families). No cases with only one black African parent have been seen.

The child of one family of South Asian descent who arrived in SA from the United Kingdom in 1998 was classified as Asian. This group would also include any South African subjects who were classified as Indian (categories '5' and '6') on hospital stickers.

All subjects were classified prior to the results of genotype testing being known.

If, as discussed above, 'races' are not genetically exclusive, yet, for certain purposes, Cape Town's non-Negroid 'persons of colour' are genetically distinct from Caucasoid populations, this method of classification, despite its dependence on a pre-existing 'race'-based system, seems the most practical in the circumstances and is likely to be sufficiently discriminating (in the scientific sense of a word that has a difficult history in SA).

The Classic Epidemiology of CF in the Western Cape Province

In the 1980s, medical staff working in the CF Clinic at the RCCH were the first to attempt to put figures to the epidemiology of CF in the then western Cape Province region.[33] The incidence rate that Hill and colleagues calculated was based on figures for CF in the population of metropolitan Cape Town. The prevalence of CF was based on all CF cases seen at the hospital and known about up to 1984. Breaking new

ground, they showed that CF was not uncommon in the coloured community. (Their definitions of these two groups were not stated but are likely to be similar to the ones I have adopted.) There was nevertheless a considerable difference in the incidence of CF between the white and coloured populations in Cape Town (1:2 027 versus 1:12 305 live births). These figures were based on the 12 white and 8 coloured children, born in 1980 to 1983, who had been diagnosed as having CF.

Prevalence figures reflected this difference. There were four times as many white as coloured cases (8,3 versus 2,1) per 100 000 of the population in urban Cape Town. A lower prevalence in rural parts of the region was ascribed to under-recognition of CF outside metropolitan Cape Town. This was noted for both groups but was especially significant in the coloured population, showing an apparent 3,5 times lower prevalence in the rural western Cape Province region compared with Cape Town. For the authors this highlighted the relative under-recognition of CF in coloured children.

Only in the 1990s was CF identified in a Xhosa-speaking black African in the Western Cape and to date only 4 such children are known to have lived in the province (see p89 below for a full description of these cases).

Motivation for the current study

1) CF birth data in Hill and colleagues' study was on a narrow base

The incidence figures for CF in the white and coloured populations in this paper were based on 12 and 8 births respectively. While the aggregation over four years would have smoothed out some variation in annual CF births, confidence intervals (CI) (not reported in the paper) were wide. For example, the incidence of 1 in 2027 (carrier rate 1 in 23) for the white population has 95% CIs of 1 in 1297 (carrier rate 1 in 18) to 1 in 4672 (carrier rate 1 in 34). For the coloured group the CIs make incidence rates even less certain: anywhere from 1 in 7246 to 1 in 38759 live births. Notably, though, the two sets of 95% CIs do not overlap suggesting a real difference in incidences despite the uncertainty of each rate.

2) The proportion of CF patients in each 'population group' has changed over time

As demonstrated in Chapter 2, the proportion of CF patients who belong to the coloured group has risen over time. This could be related to demographic change, greater relative survival or better case ascertainment in this group (in part as a result of Hill and colleagues' paper). Reviewing the incidence of CF would indicate if the latter cause explains this change.

Although they did not test their assertion statistically, Hill and colleagues' paper demonstrated that there was under-ascertainment of coloured patients in rural Western Cape areas compared with white patients. In fact their figures did *not* show under-ascertainment for white rural patients compared to urban patients (the 95%CIs for the difference spanned zero) but their statement regarding coloured rural patients was statistically true (see below p78). Whether this remains the case in an era of increased CF awareness needs to be tested.

3) There are uncertainties regarding the numerators and denominators in Hill and colleagues' study of incidence

It is uncertain where the live birth data for 'the Cape Town area' used in the paper was obtained from. They cannot be census-based as the years 1980-1983 were used and only the 1980 census mentioned as forming the basis of other calculations. If Municipal Department of Health data were used, they are unreliable. These data are reported in the Medical Officer of Health (MOH) Annual Reports and come largely from public sector facilities. They thus undercount the white group in particular. Birth registration by the Department of Home Affairs, another possible source, often lags behind the time of birth and is unreliable among poorer communities, even in urban areas.

The data on CF births I have collected cast doubt on the numerator used in the paper. The 'Cape Town area', if the former 'City of Cape Town' was meant, had 17 CF births in 1980-1983 (one of whom was not diagnosed at the time of Hill and colleagues' study), rather than the 20 they reported. If the whole of urban Cape Town was meant, the number of CF births was 26.

With Hill and colleagues' figures being the only ones available in SA, it will be important either to confirm or refute them, if it is possible to do so. Decisions about the availability of diagnostic and clinical services as well as the feasibility and utility of screening for CF have and will be made on the basis of incidence and prevalence figures. Educational strategies for health care workers are also influenced by how common a condition such as CF is. For example, if CF is really more common in the coloured population than Hill and colleagues' study suggests, efforts to change health care workers' perceptions of the likelihood of CF in certain clinical scenarios (e.g. persistent chest symptoms) will need to change.

Study 3.1 THE CLASSIC EPIDEMIOLOGY OF CYSTIC FIBROSIS IN THE WESTERN CAPE PROVINCE

Aim

To establish the incidence and prevalence of CF in the white and coloured populations of the Western Cape province of SA.

Objectives

1) To determine the incidence of CF in the coloured and white populations
2) To determine carrier rates for CFTR mutations in the coloured and white populations
3) To determine the prevalence of CF in the coloured and white populations
4) To compare these rates with those determined in the previous study from this region
5) To determine whether apparent under-recognition of CF in areas beyond the Cape Metropole and between the 'population groups' still pertains

Methods

Incidence

The number of children born with CF in Cape Town in each of the years from 1984 to 1995 was determined using data on year and place of birth from the database. As late

diagnosis is still not uncommon for CF, figures for CF births after 1995 were not used in this analysis.

The following data sets were explored in an attempt to find accurate birth data for this period: Municipal MOH Reports, Birth registration data and the 1996 population census. The municipal data for the City of Cape Town was readily available but, as discussed above, undercounted white births. It was therefore discarded and the data for Bellville and other metropolitan municipalities not sought. Birth registration has been found to be significantly low among SA's poorer and more rural populations making it a poor source for accurate birth data.[80] It was decided to use population data from the 1996 census, which, while acknowledged to have some inaccuracies for black African groups where enumerating proved to be logistically difficult, was reasonably accurate for the two populations under investigation here.[81]

The number of children between the ages of 0 and 9 years were tabulated in two 5 year groups (0-4 and 5-9 years) directly from the 1996 population census data using the CD ROMs supplied by Statistics SA.[81] These figures were equated with the number of live births in those 5 year periods and the overall 10 year period. For ease of reporting, these periods were converted into calendar years i.e. 1992-1996 = 0-4 years, 1987-1991 = 5-9 years, 1987-1996 = 0-9 years. The census was carried out in October 1996. It was assumed that numbers would not be significantly altered by this conversion. The assumption was also made that under five mortality would not have significantly altered the figures as childhood mortality was relatively low in these two groups. The 1998 Demographic and Health survey gave an overall figure of under 5 mortality for the Western Cape province of 39 and an infant mortality of 30.[82] These figures included the black African population in which higher child mortality rates than the average were found. Thus at most there would be a 0,03 – 0,04% cumulative inaccuracy (about 3-4/10 000 live births), a difference of no significance even over 10 years given the very low expected numerator in any incidence calculation for CF. The other assumption was that migration would not have significantly altered the child population figures for these two groups in the census.

The Western Cape was divided into two parts, Cape Metropole (Western Cape province Census areas 1-7 i.e. Bellville, Cape, Goodwood, Kuilsriver, Mitchell's

Plain, Simonstown, Wynberg) and non-Cape Metropole (all other areas) using the Census areas. Both CF birth and population birth data were classified according to these areas.

Incidence rates for CF (with 95%CIs) in the two parts of the province and the province as a whole were computed by dividing the number of CF births in the area by the number of live births derived from the census data and converting the fraction to a ratio. The two periods were examined separately to determine if there was consistency in the incidence rates.

Carrier rates

Carrier rates were calculated for the coloured and white populations by the formula: $\sqrt{(1/\text{Incidence})} / 2$.

Prevalence rates

Prevalence rates were determined for 1996. This was a Census year, allowing accurate determination of the coloured and white populations of the Cape Metropole and other areas of the Western Cape Province divided as for the determination of incidence (the denominators).[81] 1996 was also the year in which the study of Transition in CF reported in Chapter 8 was undertaken. This study required the names of all adults and older adolescents with CF attending the CF Clinics at GSH that, together with the RCCH database, allowed the ascertainment of nearly all patients with CF in the province and their addresses. As with the previous study of prevalence, a few cases who did not receive their care at RCCH or GSH were included (the numerators). Prevalence is reported as the number of CF cases per 100 000 of the population.

Results

The incidence and carrier rates for CF for the two periods and the two census areas together with the totals are given in Table 3.1. The proportion of CF births that were in non-Cape Metropole areas were the same for the two groups (8/31 coloured; 4/23 white, chi-square for difference = 0,54, p = 0,46).

Table 3.1 Incidence and carriers rates for cystic fibrosis in the Western Cape province

	Periods					
	1992-1996		1987-1991		1987-1996	
	coloured	white	coloured	white	Total coloured	Total white
Non-Cape Metropole areas						
Number of births	114089	17273	113989	21839	228078	39112
CF births	8	2	0	2	8	4
Incidence	1:14261	1:8637		1:10920	1:28510	1:9778
95% CI					1:16835 - 1:92593	1:4950*
Carrier Rate	1:60	1:46		1:52	1:84	1:49
95% CI					1:65-1:152	1:35*
Cape Metropole areas						
Number of births	114754	27251	121524	29815	236278	57066
CF births	9	10	14	9	23	19
Incidence	1:12750	1:2725	1:8680	1:3313	1:10273	1:3003
95% CI					1:7299 - 1:17361	1:2070 - 1:5464
Carrier Rate	1:56	1:26	1:47	1:29	1:51	1:27
95% CI					1:43-1:66	1:23-1:37
Western Cape province						
Number of births	228843	44524	235513	51654	464356	96178
CF births	17	12	14	11	31	23
Incidence	1:13461	1:3710	1:16822	1:4695	1:14979	1:4181
95% CI					1:110742 - 1:23094	1:2967 - 1:7092
Carrier Rate	1:58	1:30	1:65	1:34	1:61	1:32
95% CI					1:53-1:76	1:27-1:42

CI – confidence interval
*Only lower CI calculable

There was a significant difference in the overall incidence of CF between the white and coloured groups (p = 0.000000) in the province. If the Cape Metropole figures were taken as representing the true incidences of CF as suggested by Hill and colleagues, the difference between the groups remained (p = 0.000000).

A comparison of the incidence and carrier rates in this study and those of Hill and colleagues is given in Table 3.2.

Table 3.2 Comparison of incidence and carrier rates for cystic fibrosis in Hill and colleagues' study and this study.

	1980 – 1983 (Hill et al., 1988[33])		1987-1996 (Westwood 2004)	
Cape Metropole areas	Coloured	White	Coloured	White
Number of births	98443	24324	236278	57066
CF births	8	12	23	19
Incidence	12305	2027	10273	3003
95% CI	*1:7246 - 1:40000*	*1:1295 - 1:4673*	1:7299 - 1:17361	1:2070 - 1:5464
Carrier Rate	1:55	1:23	1:51	1:27
95% CI	*1:43-1:100*	*1:18-1:34*	1:43-1:66	1:23-1:37

Data in italics were not given in the original study
CI – confidence interval

A total of 108 CF patients were known to be living in the Western Cape province in 1996. Only one of these was a black African. Forty were coloured and 67 white. The prevalence rates for CF in the coloured and white populations for the Cape Metropole and the non-Cape Metropole areas of the Western Cape province are given in Table 3.3.

Table 3.3 Prevalence of cystic fibrosis in the Western Cape province in 1996

	Population group		
	Coloured	White	Total population
Non-Cape Metropole areas			
Population	1 016 443	331 247	1 347 690
CF patients	12	14	26
Prevalence rate / 100000	1,2	4,2	1,9
Cape Metropole areas			
Population	1 129 668	490 303	1 619 971
CF patients	28	53	81
Prevalence rate / 100000	2,5	10,8	5,0

Table 3.4 compares these 1996 prevalence figures with those derived by Hill and colleagues from 1980 census data.[33] The differences in prevalence rates between 1980 and 1996 for each population group and in each area were not statistically significant. Table 3.4 shows that prevalence of CF in the two population groups was significantly lower in the non-Cape Metropole areas in both studies with the exception of the white group in 1980.

Table 3.4. Comparison of prevalence of cystic fibrosis in 1980 and 1996.

	Coloured		White	
Non-Cape Metropole areas	1996 (Westwood)	1980 (Ref 33)	1996	1980
Population	1 016 443	634 720	331 247	219 980
CF patients	12	4	14	10
Prevalence rate / 100 000	1,2	0,6	4,2	4,5
Cape Metropole areas				
Population	1 129 668	793 020	490 303	482 240
CF patients	28	17	53	40
Prevalence rate / 100 000	2,5	2,1	10,8	8,3
Difference in prevalence between areas (95%CI)	1,3 (0,16 – 2,43)	1,5 (0,32 – 2,7)	6,6 (2,9 – 10,2)	3,8 (Not significant)

Discussion

This study aimed to have a second look at CF epidemiology in the Western Cape province. There was an opportunity to review the picture given by Hill and colleagues in the 1980s,[33] both because of doubts over some of the data in the paper and because of an apparent change in the demography of CF cases. Having a 10 year period available has allowed a consistency in incidence over time to be demonstrated. These figures are based on a database of cases that goes up to 2003. The vast majority of CF cases have been diagnosed by the age of 7 years increasing the validity of the incidence (and prevalence) figures for a period that ended in 1996. Hill and colleagues' figures were calculated at most 4 years after the years during which births were counted. The figures given here must therefore be considered to be more robust than those in the first study of CF epidemiology in this region.

Birth incidence figures may be influenced by a number of factors. This study uses clinical identification rather than any form of screening to arrive at the figures. Birth screening and screening of married couples (except where there is a family history of CF) does not occur in this area. Any systematic under-ascertainment of clinical cases would have distorted the figures. This is particularly possible in the coloured group where infant death even in diagnosed cases has been a problem. In both groups cases of CF diagnosed in adults would also not be reflected in the incidence figures in this study. To my knowledge this is not a common phenomenon in the Western Cape province (I know of one case. He was born before 1974). In recent years accurate

prenatal diagnosis has become possible. When incidence rates are converted to carrier rates the formula does not take account of cases in which affected pregnancies are terminated. Based on cases known to me, about one pregnancy every second year has been terminated for CF since the early 1990s.

This study confirms the difference in the incidence of CF between the coloured and white population groups that was first shown by Hill and colleagues.[33] In no part of the province and in none of the time periods were the incidences close to being the same.

The study also shows an apparently lower incidence of CF in non-Cape Metropole areas. Hill and colleagues related a lower prevalence rate in rural areas to under-ascertainment. There is no biological explanation for the difference in incidence as the urban and rural populations in these two groups come from the same stock so under-ascertainment is the most reasonable explanation for this phenomenon. In support of this is the apparent absence of CF births in the non-Cape Metropole coloured population in 1987-1991 compared to the 8 cases born in the next 5 year period by which time the data from Hill and colleagues study had been published and discussed. Thus the true incidences of CF were likely to approximate to those found in the Cape Metropole.

The incidence figures were similar to but not the same as those from the early 1980s. The incidence in the coloured population was lower by a factor of about 16%. More confidence can be placed in the figure of 1 in 10 273 live births as the greatly reduced 95%CI indicates. For the white population, CF would appear to have been slightly less common that the 1980-1983 figures suggested. The lower 95%CI for the 1987-1996 incidence was the almost same as the incidence of 1:2027 given by Hill and colleagues.[33]

If the same incidences are applied to the non-Cape Metropole areas as were found in the Cape Metropole areas and if full case ascertainment in the Cape Metropole is assumed, 4-5 coloured and 3-4 white babies with CF (7-9 babies in all) were born each year in the province in the period under review. Thus between 2 and 4 cases of

CF were *not* being diagnosed each year. (It should be noted that about one CF pregnancy every two years is terminated in a family with an index case.)

The study shows that carrier rates for CF were higher for the coloured group and lower for the white group than the figures used since the publication of Hill and colleagues' paper. This has implications for counselling for CF risk in these groups. (This is discussed further with the Molecular Epidemiology of CF p42.)

As presented in the Introduction to this chapter, the white population of SA, though having some admixture from other groups is largely descended from European Caucasoids. Most of these antecedents were from the northern countries of Europe. Dodge and colleagues in a thorough multicentre attempt to count every CF patient in the United Kingdom found an incidence of 1 in 2415 live births.[83] This figure is encompassed by the 95%CI for white CF births in Cape Town. Across the English channel in Brittany, recent research using neonatal screening data has suggested a similar incidence of 1 in 2838.[84] A retrospective study back to 1960 shows a similar incidence: 1 in 2640.[85] This incidence among a population with strong Celtic roots is probably not representative of the whole of France. An incidence of 1 in 3200 has been proposed for France based on three sites of neonatal screening.[86] SA's white Afrikaner population, particularly in the Western Cape province, is partly made up of descendants of French Huguenots who migrated to SA in the 17th century. This incidence is also compatible with that among SA whites. The Netherlands is the origin of a significant proportion of the Afrikaner population of SA. Recent data using the ΔF508 mutation in 11 654 blood donors has suggested that the CF carrier frequency there is 1 in 32 (95%CI 1 in 28 to 1 in 36), less than the European average of 1 in 25.[87] The South African incidence found in the Cape Town study lies between the two and the 95%CI spans both. It thus would seem that the South African incidence and carrier rates for CF for the white population correlate with those of the countries from which this population is largely derived and are not as high as Hill and colleagues suggested in 1988. There is therefore no sign of genetic drift or heterozygote advantage or disadvantage for this disease in SA.

The coloured families in this study would appear to be representative of the population they came from. Only two families had a 'pure' Caucasoid parent (one

from England; one an Afrikaner); none had a 'pure' black African parent. The significantly lower incidence in this group compared to the white group suggests that CF genes were less common in the KhoiKhoi, West and East African and East Asian antecedents of this group. Cases of CF and CFTR mutations are known to be rare in the latter two groups. Of the 'original' inhabitants of the Cape, the San have not been shown to have CFTR mutations. Padoa and colleagues, in their study of CFTR mutations in Africa, did not find any mutations in 208 healthy San subjects.[50] Populations with dominant KhoiKhoi antecedents such as the Griqua and the Nama have not been studied in this respect.[50] It is likely therefore that the difference demonstrated in this study, though probably smaller than that suggested by the original study of Hill and colleagues, was real and was not a product of under-ascertainment. (Further light on the origins of CF in this group is shed by the study of the Molecular Epidemiology of CF reported on p42.)

Prevalence rates for CF depend on the number of cases diagnosed and their survival. As Table 3.1 shows, there was a 3,4 fold difference in the incidence of CF between the white and coloured groups. The prevalence of CF in the Cape Metropole, however, was over 4 fold higher in the white group compared to the coloured group. Greater early mortality in the coloured group, as demonstrated in my 1999 study of the prognosis of CF in the Western Cape province (reproduced in Chapter 9 p250), is likely to explain this greater difference.

For both groups CF prevalence was about 2,5 times lower in rural than urban areas. For the white group in 1996, unlike in 1980, this was statistically significant. This urban/rural difference in prevalence rates probably reflects the under-ascertainment demonstrated by the incidence data, but a greater rural mortality may also be a factor given problems with access to specialised health care experienced by poor South Africans.

The study was unable to demonstrate a change in the prevalence of CF in 16 years even in the Cape Metropole. If there is a trend to increased prevalence as the figures suggest, increased longevity is likely to have been responsible as incidence will not have increased over the two decades.

These prevalence data make it possible to estimate the number of CF patients from the coloured and white groups in SA. Using data on the national population from the 2001 National Census,[88] there would have been 100 coloured and 464 white persons with CF in the country in 2001; a total of 564 (Table 3.5). Thirty nine of the expected 100 coloured persons in SA were known in the Western Cape in 2003. According to the 2001 Census, 61% of SA's coloured population live in the Western Cape province. Table 3.5 shows that 61 (95%CI 46-76) coloured CF patients would be expected in the province. The apparent absence of over a third of them suggests that, even in 2003, CF is being missed in this group, presumably largely in non-Cape Metropole areas. Chapter 2 showed the increasing proportion of coloured patients at the RCCH CF Clinic (p19). The CIs in Table 3.5 suggest that the number of white and coloured CF persons in the province may even be about equal.

Table 3.5 Expected numbers of coloured and white persons with cystic fibrosis in South Africa in 2001

	Coloured		White		Total
	Population	Persons with CF (95%CI)	Population	Persons with CF (95%CI)	Persons with CF (95%CI)
Eastern Cape	478807	12	304506	33	45
Free State	83193	2	238791	26	28
Gauteng	337974	8	1758398	190	198
KwaZulu Natal	141887	4	483448	52	56
Limpopo	10163	0	126276	14	14
Mpumalanga	22158	1	203244	22	23
Northern Cape	424389	11	102043	11	22
North West	56969	1	244035	26	28
Western Cape	2438976	61 (95%CI:46-76)	832901	90 (95%CI:71-108)	151 (95%CI:127-175)
Total	3994516	100 (95%CI:80-119)	4293642	464 (95%CI:421-507)	564 (95%CI:517-611)

Table 3.5 shows the number of coloured and white persons with CF expected in each of SA's provinces in 2001. Gauteng would expect the largest number of persons with CF, almost all of whom would be white. The figures in this table assume that prognosis of CF in all the provinces was about equal and therefore may reflect higher numbers than the actual number of persons with CF in provinces in which the condition has a poorer prognosis than in the Western Cape province. There is no data on which to take this issue further.

This study has only taken account of coloured and white persons with CF. CF is rare in Asians and only one such patient has ever attended the Cape Town CF Clinics. CF among black Africans is the subject of much conjecture and debate since Padoa and colleagues suggested that carrier rates were possibly as high as in other populations groups in SA.[50] Only one black CF patient was known in the Western Cape in 1996. The Classic Epidemiology model is unable to give incidence and prevalence data in this group. It can only ask the Molecular Epidemiology model that was used by Padoa and colleagues where all the expected black African CF patients were. This the Molecular Epidemiology model will attempt to answer (p51).

In conclusion, this study has established new incidence figures for CF in SA in the coloured and white groups. It has confirmed that there is a difference in the incidence and prevalence between the groups and that rural under-ascertainment of CF cases was occurring in both groups in 1996. The prevalence of CF in the Western Cape province may be rising.

The Molecular Epidemiology of cystic fibrosis in the Western Cape province

Soon after the identification of CFTR it became clear that, at a molecular level, CF was a heterogeneous disease.[89] Although one mutation, ΔF508, dominated in the first CF populations investigated with the new molecular tool, many CF-causing mutations were soon found, confounding hopes that molecular methods would provide a simple diagnostic tool and that a genetic cure might lie within reach.

This expanding evidence of the genetic heterogeneity of CF led to the discovery that populations of differing genetic histories carried different patterns of CF mutations. The earliest evidence of this was found in Europe.[90] There was a decreasing proportion of CF patients with ΔF508 the further South they lived.[91] For those in northern Europe e.g. in Denmark, the frequency of ΔF508 was 88% whereas in the southern Europe, e.g. Albania, it was 52% with other CF-causing mutations making up the remainder. Certain mutations were found to be specific to certain populations e.g. 394delTT in Nordic countries and Q359K/T360K among Jews in Georgia.[92]

The molecular basis of cystic fibrosis in South Africa

The molecular basis of CF in South African populations has now been well studied. The first studies following the identification of CFTR pursued haplotype analysis and ΔF508. Initial work by the South African Institute for Medical Research (SAIMR) at the University of the Witwatersrand was reported in a letter to the *American Journal of Human Genetics* published in 1990.[93] This letter was written by the Cystic Fibrosis Genetic Analysis Consortium and contained the results of a worldwide survey of ΔF508. Thirty six CF chromosomes from Caucasoids had been screened in Johannesburg and 27 (75%) had ΔF508.

In the same year a study of DNA from South West African Afrikaners with CF was presented.[94] These six patients had been studied by Super in the 1970s, before the country's name was changed to Namibia. Eight (67%) of the 12 chromosomes had ΔF508 showing the mutation to be common among Afrikaners.

Groups from within SA reported their experience with the molecular genetics of CF in an edition of the *South African Medical Journal* in 1992. A study from the Department of Human Genetics at Tygerberg Hospital in Cape Town described patients from the RCCH CF Clinic.[45] DNA from 71 white and coloured patients was studied. Tables 3.6 and 3.7, reproduced from this study, show the frequencies of ΔF508 and of genotypes in the two populations.

Table 3.6 Number and proportion of the ΔF508 mutation in 142 mutant cystic fibrosis genes from 71 cystic fibrosis patients (after Herbert and Retief 1992[45])

	Frequency of mutations in CF genes		No. of CF genes
Ethnic group	ΔF508	Other	
White	0,82 (94)	0,18 (20)	114
Coloured	0,53 (15)	0,47 (13)	28
Total	**0,77 (109)**	**0,23 (33)**	**142**

Other refers to mutations in CF genes other than ΔF508 mutation. The number of CF genes is indicated in parentheses

Table 3.7 Genotypes of 71 cystic fibrosis subjects (after Herbert and Retief 1992[45])

	No. of CF subjects per genotype			
Ethnic group	ΔF508 / ΔF508	ΔF508 / other*	Other*/ other*	No. of subjects
White	39 (68)	16 (28)	2 (4)	57
Coloured	3 (21)	9 (64)	2 (15)	14
Total	**42 (59)**	**25 (35)**	**4 (6)**	**71**

*Other refers to mutations in CF genes other than ΔF508 mutation. Percentages are indicated in parenthesis

The high frequency for ΔF508 in CF chromosomes from white patients was also shown in the other studies reported in that *SAMJ* edition. Geneticists from Johannesburg reported on 81 families and found an 82% prevalence of ΔF508.[43 44] This study also shed light on the origin of most white CF families. Haplotype analysis of the CFTR region coincided with those found in chromosomes from northern European persons.

The relatively low rate of 53% for ΔF508 in CF chromosomes in coloured patients indicates a different genetic background. Only one third of coloured patients were homozygous for ΔF508 compared with two thirds for whites. It should be noted that frequencies for the coloured group were based on 28 chromosomes (14 patients). CIs reveal that the difference between white and coloured patients in terms of ΔF508 frequency may not have been as great as given unanalysed in Herbert and Retief's Tygerberg paper (Tables 3.6 and 3.7).[45] The 53% figure for the coloured group has a wide 95%CI at 34 to 72,5%. The 95%CI for the 82% of CF chromosomes from white

patients is 75,5 to 89%. Likewise the difference between the rates of homozygosity for ΔF508 (21%) and compound heterozygosity (64%) in the coloured group, i.e. 43, could be as little as 9 or as much as 76. It would be important to have frequencies on a larger number of CF chromosomes from coloured patients before these figures could be taken as representing the situation precisely.

The place of genetic testing for CF and the counselling implications were discussed in detail in these articles.[43-5] ΔF508 testing was noted as a great advance that would replace much of the restriction fragment length polymorphism (RFLP) analysis that had guided most genetic counselling regarding carrier status and prenatal counselling up till then. It was noted that, owing to its lower prevalence in the coloured population, ΔF508 testing was going to be less informative in this group. Screening for CF in the SA context was thought to be impractical on the basis of the data from these studies.

As Denter and colleagues put it in the conclusion of their paper:

> "It is highly desirable to determine which mutations occur in southern Africa, and at what frequency in order to improve carrier detection and the accuracy of risk calculation."[44]

World wide through the 1990s, dozens of new disease-causing CFTR mutations were identified. Which ones would be informative in SA? In particular, which ones would help in identifying the genetic basis for CF in coloured patients and so fulfil the hopes expressed in 1992?

Rather unexpectedly, a big step forward was made through the study of a number of black African patients with CF who were diagnosed in the 1990s.[49] This research is described in detail on p62 in the section of this chapter discussing CF in black Africans in the Western Cape Province. The important outcome for the understanding of the Molecular Epidemiology of CF in the coloured population was the identification of one common mutation in black African patients: 3120+1G→A.

The next phase in the understanding of the Molecular Epidemiology of CF in SA came through the application of panels of the more common CFTR mutations (including 3120+1G→A) to local CF chromosomes.

This analysis was largely performed in Johannesburg by the SAIMR at the University of the Witwatersrand in collaboration with CF workers in SA and laboratories in France and Germany. These studies, which have given cumulative insight into the Molecular Epidemiology of CF in SA, were published in 1994, 2001 and 2003.[46-8] They are summarised in Table 3.8 and show a progressive refining of knowledge in this area.

Table 3.8 CFTR gene mutation analysis in chromosomes from South African cystic fibrosis patients: 1994, 2001, 2003

	Goldman et al 1994 (Reference 46)		Goldman et al 2001 (Reference 47)			Goldman et al 2003 (Reference 48)		
	White (N* = 250)	Coloured (N = 2)	White (N = 384)	Coloured (N = 28)	Black (N = 24)	White (N = 402)	Coloured (N = 86)	Black (N = 28)
	Frequency of mutations							
Mutation								
ΔF508	80,4	50	76	42,9		76	50	
3272-26A>G			4			4	1,2	
394delTT			3,6			3,7		
G542X	1,2		1,3	3,6		1,7	2,3	
R553X	0,4		1			1		
W1282X			1			1		
N1303K	0,4		1			0,8		
G551D			0,8	3,6		0,25	2,3	
3120+1G>A			0,5	28,6	45,8	0,5	17,4	46,4
R117H			0,3			0,25		
Q493X			0,3			0,25		
S549N	0,4		0,3			0,25		
621+1G>T	0,4		0,3			0,25		
1717-1G>A			0,3			0,25		
2789+5G>A			0,3			0,25		
3659delC								
R1162X				3,6			1,2	3,6
G1249E					4,2			3,6
3196del54					4,2			3,6
94G>T					4,2			3,6
2183delAA					4,2			3,6
Unknown	16,8	50	9,1	17,9	37,5	8,6	25,6	39,3
Total detected			**90,9**	**82,1**	**42,5**	**91**	**74,4**	**60,7**

* N is the number of chromosomes tested

ΔF508 is the dominant mutation in the white population of SA with a frequency of 76% in CF patients.[48] This is less than the frequency of 81 or 82% reported on fewer patients in 1992. Sixteen mutations account for 91% of CFTR mutation in the white population. In the coloured population ΔF508 is the commonest mutation (50%) with the 3120+1G→A mutation being significantly common at 17,4%. Six mutations account for 74,4% of CFTR mutations in this population.

AFRICA'S BIG TWO: A Description of the two commonest CFTR gene mutations in southern Africa

Delta F 508

With the identification of the CF gene in 1989 came the discovery of the common mutation that had been predicted by haplotype analysis.[14 15] This was a three base pair deletion in exon 10 of the CF gene that led to the absence of phenylalanine at position 508 in the as yet unnamed protein product, later CFTR. The shorthand for this is ΔF508 and it accounted for 70% of mutant genes in the initial study. ΔF508 was common in Caucasoids, particularly those living in north west Europe and North America. Haplotype analysis had already suggested that this mutation had been a once-off phenomenon. Study of ΔF508 among European populations indicated that it probably originated in older European populations as demonstrated by the prevalence of 87% in people of pure Basque descent and spread to the new immigrants from the South East.[95]

The clinical correlate of ΔF508-associated CF had been anticipated by haplotype studies in 1989.[96] These showed that the dominant haplotype-associated mutation was associated with pancreatic insufficiency (PI) whereas with many other CF-associated chromosomes pancreatic sufficient (PS) forms of CF were more common. This was confirmed by the Canadian group in Toronto (who must have been working feverishly hard at this exciting time). In a paper published in the *New England Journal of Medicine* in 1990, ΔF508 homozygosity was shown to be almost always (99%) associated with PI whereas PS occurred in 72% and 36% of ΔF508 compound heterozygotes and patients with no identified mutation respectively.[97] Further correlations between the ΔF508 homozygous genotype and clinical features of CF were found: meconium ileus (MI), high sweat chloride concentrations, earlier diagnosis. As PI itself was associated with worse lung disease and nutritional status, ΔF508 was characterised as a 'severe' mutation i.e. homozygosity for ΔF508 meant severe disease in almost all cases, compound heterozygosity of the mutation leading to mitigation of its 'severe' nature in some cases.

This hopeful prediction (i.e. better outlook for ΔF508 compound heterozygotes) was disproven in a large study comparing ΔF508 homozygotes with compound heterozygotes for ΔF508 and 7 non-ΔF508 mutations.[98] No differences were found between the two groups except for the ΔF508/R117H genotype in which PS was the rule. Notably pulmonary function, even between ΔF508 homozygotes, was very variable. These findings have been established as correct across other Caucasoid populations.

ΔF508 has not been found in populations amongst whom CF is rare: American Indians, black Africans, Asians.

In summary ΔF508 is the commonest CFTR mutation in most European Caucasoid populations. It is associated with PI and other gastrointestinal conditions in homozygotes. Most homozygotes will have significant pulmonary disease.

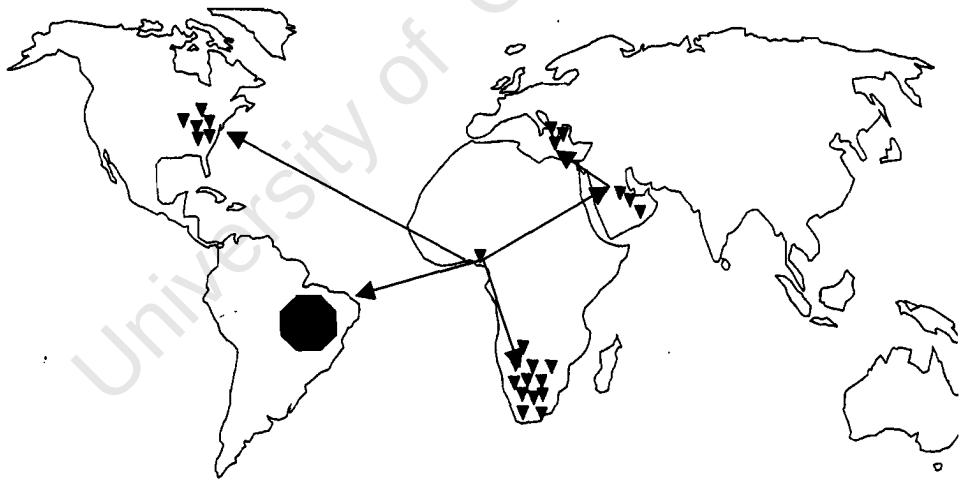
3120+1G→A

The 3120+1G→A mutation, though much less common worldwide than ΔF508, assumes a greater role in non-Caucasoid populations.[99] It is a splicing defect in intron 16 owing to a change from guanine (G) to adenosine (A) at position 3120+1. That it was a mutation rather than a polymorphism was indicated by its absence in a large number of normals and CF carriers. It is very rarely found in Caucasoids but is present in 12,2% of African American CF chromosomes.[99] Macek and colleagues who have conducted the largest study of African American CF mutations showed that, if 'Caucasoid' alleles were excluded, 3120+1G→A would be responsible for 53% of African American alleles.[99] Even more significantly, it has comprised 5 out of 8 CF mutations in 4 black African children with CF.[49]

The mutation is also found in Brazil.[100] In Rio de Janeiro it was the second most common mutation after ΔF508 (ΔF508 25,7%, 3120+1G→A 4%), reflecting the priority of this mutation as found in African Americans. Negroid admixture in the city was 52% suggesting an African origin for the mutation in this population.

3120+1G→A was first identified in three African Americans with CF and was the first of a number of mutations that were initially found in Negroid populations.[99] However it is not exclusive to them. It was identified in Arabs in Saudi Arabia in 1997.[101] It constitutes 10% of known CFTR mutations in that country but, of the 7 families with the 3120+1G→A mutation, only 3 (all homozygotes for the mutation) were Saudi. The nationalities of the other families were not given. The mutation has also been found in a Bahraini Arab family.[102] In Europe the mutation has only been found in Greece where it constituted 3 out of 500 CF chromosomes from Greek patients.[103]

Figure 3.1 Sites in which the 3120+1G→A mutation has been found (adapted from Reference 104.



That this mutation appeared so common in Negroid populations yet was also found in southern Europe and Saudi Arabia (see map Fig 3.1) led to a study of haplotypes to test whether the mutation had a common origin or was the result of multiple mutational events.[104] Strong correlations between the Arab, African and African American haplotype patterns were found suggesting a common origin. The Greek haplotype, while it differed in a minor way from the others, was not thought to be different enough to be explained by a second mutational event. "Gene flow" across the Sahara is known to have brought spread of other genetic disease and CF seems to have been no exception and

3120+1G→A is the evidence. Its presence in Brazil is likely to relate to the slave trade from West Africa in the 17th and 18th centuries.

Analogous to the relationship between the ΔF508 and 3120+1G→A mutations amongst African Americans, though for different historical reasons, the two mutations dominate the molecular biology of CF in the coloured population of SA. Between the two, they accounted for 67% of mutations in the coloured population in the most recent study of CF in SA.[48] The origin of the 3120+1G→A mutation in this population is thought to be Negroid.

The 3120+1G→A mutation has now been found in black African heterozygotes. Carrier rates of 1 in 91 have been found in southern Africa leading to questions regarding the apparent rarity of clinical CF amongst black Africans in the area.[50] This is discussed in detail with Study 3.3.

In summary the 3120+1G→A mutation has earned the epithet of the 'African mutation' and it is appropriate. Its identification may have opened the way to a change in our understanding of the epidemiology of CF in Africa.

Study 3.2 THE MOLECULAR EPIDEMIOLOGY OF CYSTIC FIBROSIS IN THE WESTERN CAPE PROVINCE

Aim

To describe the Molecular Epidemiology of CF in a Western Cape CF population.

Objectives

1) To determine the prevalence of ΔF508 in the white and coloured patients in this Western Cape CF population
2) To determine the frequency of other CFTR mutations in the white and coloured patients in this CF population
3) To determine the prevalence of homozygosity and compound heterozygosity for the two common mutations (ΔF508 and 3120+1G→A) and undetermined genotypes in the white and coloured patients in this CF population.

Methods

Study population

The CF population described in Chapter 2.

Data

Genotype information from the CF database. Patients' genotypes had been determined using a number of laboratories:

The RCCH which tested for ΔF508 and, when kits were available, other CFTR mutations[105];

The SAIMR in Johannesburg who undertook testing in both the course of clinical work and in studies of the Molecular Epidemiology of CF coloured patients in SA;

A private laboratory associated with the University of Stellenbosch at Tygerberg Hospital, Cape Town.

The mutation analysis of patients who settled in the Western Cape Province from elsewhere was taken from referral letters where available.

Where mutation analysis was done beyond simply testing for ΔF508, it usually consisted of a panel of mutations found to be significantly common in South African populations. Formal testing of every patient could not be undertaken.

Analysis

Data was analysed in the format used in Goldman and colleagues' 2003 paper[48] and Herbert and Retief's 1992 paper[45] i.e. mutation frequency by population group and genotype frequency according to the presence or absence of ΔF508. Proportions and differences in proportions between the white and coloured groups were subjected to confidence interval analysis (Confidence Interval Analyser Version 1.0, Gardner GM, BMJ Publishers 1989)

Results

Of the 181 patients in the CF population, 176 were in the white (101) and coloured (75) groups. Fourteen siblings (5 white and 9 coloured) were excluded from this genetic analysis as they were presumed to have identical mutations. Twenty four

(14,8%) of the remaining 162 patients (16 white and 8 coloured) did not have any mutation analysis. Nineteen of these had died or moved elsewhere before testing became possible; in five cases, genetic testing had not been indicated by reproductive or diagnostic questions. Of the 138 (80 white, 58 coloured) who had some form of mutation analysis, 107 (77,5%) were only tested for ΔF508. Thirty one (22,5%) (21 coloured) patients who were not ΔF508 homozygous had had more extensive mutation analysis.

Mutation analysis

In all therefore, 276 chromosomes were tested, 160 from white patients and 116 from coloured patients. Table 3.9 shows the number and frequency of CFTR mutations in these two groups.

Table 3.9 Frequency of CFTR mutations in white and coloured cystic fibrosis patients in the Western Cape province

	White		Coloured	
	Number (N = 160)	Frequency (95%CI)	Number (N = 116)	Frequency (95%CI)
Mutation				
ΔF508	126	0,79 (0,72-0,85)	55	0,47 (0,38-0,57)
3120+1G>A			12	0,10 (0,05-0,16)
G551D	2	0,012	2	0,015
G542X			1	0,0075
A455E	2	0,012		
W1282X	1	0,006		
N1303K	1	0,006		
394delTT	1	0,006		
3272-26A>G			1	0,0075
Unknown	27	O,17	45	0,39
Total detected	133	0,83 (0,77-0,89)	71	0,61 (0,52-0,70)

The frequency of ΔF508 versus all other mutations for the two groups is shown in Table 3.10. Ninety two percent (95%CI 84-97) of white patients had at least one copy of ΔF508 compared with 71% (95%CI 57-82) of coloured patients.

Table 3.10 Frequency of the ΔF508 mutation versus other mutations in the white and coloured cystic fibrosis patients

	Frequency of mutations in CF genes		No. of CF genes
Ethnic group	ΔF508	Other	
White	0,79 (126)	0,21 (34)	160
[95%CI]	0,72 - 0,85	0,15 - 0,28	
Coloured	0,47 (55)	0,53 (61)	116
[95%CI]	0,38 - 0,57	0,44 - 0,62	
Total	**0,66 (181)**	**0,34 (95)**	**276**

Other refers to mutations in CF genes other than ΔF508 mutation. The number of CF genes is indicated in parentheses

Genotypes

The genotypes of the two groups according to ΔF508 status are shown in Table 3.11. The difference between the percentage of coloured patients who were homozygous for ΔF508 (24) and those who were heterozygous for the mutation (47) was 23 (95% CI 6-39). Ten coloured patients had the 3120+1G→A mutation: 6 patients (10,3% 95%CI 3,7-21,2%) had the ΔF508/3120+1G→A genotype; 2 had the 3120+1G→A mutation in combination with another mutation; 2 were homozygous for this mutation.

Table 3.11 Frequency of genotypes in coloured and white cystic fibrosis patients

	No. of CF subjects per genotype			
Ethnic group	ΔF508 / ΔF508	ΔF508 / other*	Other*/ other*	No. of subjects
White	52 (65)	22 (27,5)	6 (7,5)	80
Coloured	14 (24)	27 (47)	17 (29)	58
Total	**70 (46)**	**58 (38)**	**24 (16)**	**138**

*Other refers to mutations in CF genes other than ΔF508 mutation. Percentages are indicated in parenthesis

A full genotype was available for 59 (74%) white and 26 (45%) coloured patients i.e. 85/138 (62%) CF patients. If siblings were included, the number of patients with full genotypes was 93/162 (57%).

Discussion

Molecular genetic studies of CF in SA in the CFTR era started with explorations of the role of the ΔF508 mutation in SA.[43-5] These studies were published in 1992 and showed "European" levels (>80% of chromosomes) of the ΔF508 mutation in white CF subjects. The mutation was significantly less common in SA's coloured population (53%). By 2003 it was possible on a national scale to identify full genotypes for 83% of white CF patients and 55% of coloured patients if the mutation panels developed by the SAIMR in Johannesburg were used.[48]

The present study reproduces the regional work on ΔF508 of Herbert and Retief that was published in 1992[45] but with a much larger patient base from the Western Cape province. The study aimed to describe the pattern of CFTR mutations in the region using patient related data. It was therefore not a systematic study in the form of the SAIMR studies discussed in the Introduction to this section. However the demographics of the Western Cape are such that the data for coloured patients is unique. Herbert and Retief's study had 14 coloured patients. The latest SAIMR report had 43 patients.[48] The present one has 58. Apart from ΔF508, CFTR mutations that have been found in white CF patients in the Western Cape have not previously been described (except in one family[105]) although some are embedded in the SAIMR data.

For white CF patients, the rate of the ΔF508 mutation among CF chromosomes and the rate of ΔF508 homozygosity coincide with those given by the SAIMR and a decade ago by Herbert and Retief (but now with tighter 95%CIs).[45] The SAIMR's study with the largest number of chromosomes (384), published in 1994, showed a ΔF508 frequency of 0,76,[46] well within the 95%CI presented here. Likewise the ΔF508 homozygosity rate in the SAIMR study published in 2001 was coincident with that presented here at 64,5%.[47] These rates mirror those of northern Europe as the authors of the 1992 reports noted.

Very few white patients had been tested for other mutations. The mutations found are all in the SAIMR panel.[48] The 3120+1G→A mutation was not found in a white subject. One such patient was found in Johannesburg. There is no reason to suspect

that the mutation detection rate of 0,91 that the SAIMR has achieved in white subjects could not be achieved in the Western Cape province. However with access to excellent sweat testing and with a ΔF508 homozygosity rate of 65%, it seems unnecessary in diagnostic terms to extend the range of mutations routinely tested for in this population in this region. For genetic counselling and antenatal testing in affected families, the figures given by the SAIMR in 2003 are the best available and allow much more precise estimates of risk than ΔF508 alone can achieve. Further testing would be dictated by the circumstances of the individual family.

This study allows a more precise value for the frequency of the ΔF508 mutation in the coloured group to be given than previous work allowed. The frequency of 0,52 shown by Herbert and Retief[45] is encompassed by the 95%CI given here but the 95%CI is much narrower. The 0,5 frequency for the ΔF508 mutation given in 2003 by the SAIMR (and which included a number of patients from the Western Cape province) has a 95%CI of 0,39-0,61,[48] a little wider than in this report. In practical terms the latter difference is insignificant and a frequency of about or just under 0,5 can be accepted.

The new figures prove that there are more coloured compound heterozygotes for ΔF508 than homozygotes though the difference may not be large. There were too few patients in Herbert and Retief's study to prove this. At 24% homozygosity, testing for the ΔF508 mutation to diagnose CF must be considered inadequate in this group.

Even with the new figures, one cannot be certain that there is a difference between the proportion of those who were heterozygous for the ΔF508 mutation (47% 95%CI 33-60) and those who did not have a copy of the mutation (29% 95%CI 18-43). Importantly, at 29%, the absence of the ΔF508 mutation is more common in a true coloured CF patient than the unanalysed figure of 15% given in 1992 had suggested. The practice of 'screening' patients with symptoms of CF with a ΔF508 test cannot be supported.

With ΔF508 being a poor indicator of CF in the coloured population, what is the value of the other CFTR mutations in diagnosing CF? The 3120+1G→A mutation has proven itself to be an important player in CF in this group. Ten of the 58 coloured

patients, only 21 of whom had been tested, had at least one copy. Of the 86 chromosomes from coloured CF patients tested by the SAIMR, 15 (frequency 0,174 95%CI 0,1-0,27) had the mutation.[48] Combining the SAIMR frequency for the 3120+1G→A mutation with the frequency of ΔF508 from this study, 64% of chromosomes would be identified as abnormal with an upper confidence limit of 84%. Only 38% of coloured subjects had their full genotype delineated by testing for these two mutations. These frequencies are not enough to make testing for the two mutations diagnostically useful. In the 2003 SAIMR study in which all except 5 of the 43 coloured subjects were examined using the full South African mutation panel, 55% had both mutations identified.[48] There is a need to explore the role of this mutation in the coloured population further as frequencies are not yet precise enough. No other mutation yet identified has proved significantly common in this group. In the meantime, the sweat test must remain the gold standard for CF testing in coloured patients. Mutation analysis should be reserved for informing reproductive choices in affected families.

The 3120+1G→A mutation has convincingly been shown to be of African origin.[104] Its presence at a significant frequency in the coloured population therefore speaks of a significant frequency of African genes in this group. All other mutations identified in this group have been well described in European Caucasoids with CF. It is difficult to be sure whether the mutation entered the Cape through West Africa (slaves brought to the Cape) or via the southern extension of the Bantu expansion. A third possibility exists that might explain its presence in this group. It is not impossible that the mutation already existed in the Cape at the time of European colonisation though there is no evidence of this. The mutation was not found in 208 San subjects.[50] It was not found in 52 Xhosa subjects, a group in whom there is significant Khoisanid admixture.[50] However some anthropological theories have the KhoiKhoi migrating as far as West Africa where the mutation is hypothesised to have originated.[76] Could it in fact have originated in the Cape and could the mutation frequency of 0,174, which translates to a carrier rate of 1 in 291 (51x(1/0,174)) among healthy 20th century coloured subjects, be a reflection of a *diluted* background significant carrier rate among the KhoiKhoi of the 17th century? Padoa and colleagues found a frequency for this mutation among southern African healthy black subjects of 1 in 91 (95%CI 1 in

46 to 196).[50] The meaning of these figures for the Western Cape province is discussed in terms of the Cape's black African population on p71. Suffice it to say here that the uncertainty of these figures for individual chiefdoms means that they cannot prove that the 3120+1G→A mutation came into the coloured population of the Cape via the most southward extension of the Bantu expansion.

In their 1992 papers on CF in SA in the light of new knowledge of the ΔF508 mutation, the geneticists from Johannesburg and Cape Town explored the implications of their work (which incorporated the epidemiological work of Hill and colleagues[33]) for genetic counselling.[43-5] Risk estimates for an individual being a carrier of a mutation for CF or having a child with CF were given in various clinical settings were calculated. The revisions to the classic and molecular epidemiology of CF in SA over the last decade presented in this chapter mean that these figures have changed.

An example will illustrate this change. In Family B in Denter and colleagues' second 1992 paper,[44] the sibling of a deceased CF child was 8 weeks pregnant. She and her husband did not carry the ΔF508 mutation. Their risk of having a child with CF was 2/3(the chance that the mother was a carrier)x3/10(the chance that she had a non-ΔF508 mutation [this figure was more conservative than the 2/10 risk their study had shown])x1/23(the probability that her husband was a carrier)x3/10(the probability that he had a non-ΔF508 mutation)x1/4(the probability that two CF carriers would have a child with CF) i.e. 1:1534. Using the latest figures, this formula would read: 2/3x24/100x1/27x24/100x1/4 i.e. 1:2812, a considerably smaller risk. If the panel of SA CFTR mutations was tested for in both spouses, the risk would fall to 2/3x1/10x1/27x1/10x1/4 i.e. 1:16200. Similarly for a coloured family, if both parents were ΔF508 negative, the risk would be 2/3x5/10x1/51x5/10x1/4 i.e. 1:1224. If the 3120+1G→A mutation was added to the screen in this coloured family, the risk would halve to 2/3x33/100x1/51x33/100x1/4 i.e.1:2810 – almost identical with the risk in a white family tested for ΔF508 alone!

For a known CF carrier in the coloured population, the exclusion of the ΔF508 and 3120+1G→A mutations in the prospective spouse with no family history of CF would give a risk of having a child with CF of ½(the chance of carrier passing on their

mutation)x1/51(the chance of the spouse being a carrier)x33/100(carrier risk for another mutation in that spouse)x½(the chance of the spouse passing on their mutation) for each pregnancy i.e. 1:612. The risk if only ΔF508 was excluded would be 1:408. The equivalent figure in Herbert and Retief's 1992 paper was 1:468.[45] The addition of the 3120+1G→A test and the new carrier figure for the coloured population therefore make it possible to give a considerably reduced risk to prospective parents. Use of the full panel of mutations reduces the risk to 1:816. In individual settings the costs of these various options would have to be taken into account.

In essence, then, knowledge of the classic and molecular epidemiology of CF among the white and coloured populations of the Western Cape province has revised one's view of the disease in this region. Almost as many coloured as white patients would be expected. Affected children (and probably adults) are being missed in areas beyond metropolitan Cape Town. Informative molecular genetic testing has moved beyond testing for ΔF508 alone. All decisions around counselling and testing need to take account of this new knowledge.

But what of the epidemiology of CF in the other major population group in the Western Cape, blacks of African origin? Four cases from this group were seen among the 181 CF patients. Is CF as rare as has always been thought in this group? The following section explores these questions.

Cystic fibrosis among Negroid populations

That CF was much less common in Negroid peoples than among Caucasoids was noted early in the understanding of CF as a genetic and clinical entity.[89] In fact as senior a figure as Steinberg, the editor of the *American Journal of Human Genetics* in the 1950s, stated in an article on the epidemiology of CF that it was most likely that CF did not occur in black Americans.[106] However it was soon to be shown that it did occur in this population. Di Sant'Agnese noted in 1961 that only 4% of CF patients in his New York clinic were black despite the community served by the hospital being 30% black.[107] Kulczycki and colleagues described 9 patients in Washington in 1964, noting early mortality.[108] After an active search for cases, enough black CF patients

had been identified in this area by 1974 for Kulczycki and Schauf in Washington DC to estimate an incidence of 1:17 000, considerably less than the 1:1 000 to 1:3 500 for Caucasoids.[109] However this figure was based on only eight births. Stern from Cleveland reported 17 patients over nearly 20 years.[110] This apparently low incidence was further refined to 1:15 000 using data from the CF Foundation National CF Patients Registry.[111] This registry carried data on 601 African American CF patients in 1994. Up to this time reports on CF in other Negroid populations only came in the form of case reports (See p62).

CF in the African American population

The African American population is considered to have a significant Caucasoid admixture. Reed estimates this to be about 20%.[112] This makes this population a poor basis for prediction of the incidence of CF in other Negroid populations. This Caucasoid admixture was confirmed when African American CF patient's 7th chromosomes were compared with those from Caucasoids.[89] Haplotype analysis showed that there was to some extent a different haplotype frequency in black chromosomes compared to that pertaining to chromosomes from Caucasoids. Notably, though, the overlap was significant enough for them to calculate that

> ....one might predict that Caucasian genes account for 50% or more of the CF genes in American blacks.[89]

This prescient statement took place before the identification of CFTR. Once the new molecular methodologies became available in 1989, Macek and colleagues investigated the CFTR mutations in 82 chromosomes from black CF patients, all except one of whom (a Cameroonian) were African Americans.[99] Remarkably, they confirmed the earlier estimate: 52% of mutations were Caucasoid mutations. A further 23% were specific to Negroids and 25% could not be identified, suggesting extreme rarity. Dominant among the Negroid mutations was 3120+1G A (12,2%) which has already been discussed for its role in CF causation in coloured CF patients in the Western Cape province. Thus it is confirmed for those working with other Negroid populations that the African American experience with CF epidemiology cannot be expected to parallel that found elsewhere.

Could the same be said for the *clinical* manifestations of CF in Negroid populations elsewhere? Are they distinguishable from the features of CF in Caucasoids? From an early stage the clinical features of CF in African Americans were compared with their Caucasoid counterparts in an attempt to answer this question. Until recently the answers were equivocal or contradictory, owing to limited case numbers.

Kulczycki and Schauf, in Washington, reported in 1974 that gastrointestinal manifestations of CF dominated the presentation of CF in African Americans.[109] Stern and colleagues in Cleveland also noted significant amounts of MI (6/17 patients) in 1976 and all their African American patients were PI.[110] Lung disease was though to be mild when compared with that in white Americans.

In 1991 McColley and colleagues reported the Baltimore experience with African American CF patients.[113] They compared 24 of them with 48 matched white CF patients. They found few differences. Only hyponatraemic dehydration and peptic ulcer disease differed, being higher among the African Americans. They noted a predominance of respiratory presentations rather than the gastrointestinal ones noted in the earlier reports. Genetic heterogeneity was postulated as the reason for the differences because at that time

> ...a number of mutations were found and only a relatively small number of subjects had gene analysis, [they] were unable to correlate specific mutations with disease severity.[113]

It took the large Registry-based study reported in 1997 to bring a steadying hand to this confusion arising from small series.[111] Out of 601 African American CF patients, 47 were homozygous for ΔF508. These patients were each matched with 4 white homozygotes. Notably, the nutrition measures of the African Americans were worse. Lung function was equivalent as were the presence of PI (95,7%), *P aeruginosa* and *A fumigatus* colonisation, MI and the distal intestinal obstruction syndrome.

When all 601 African American patients were compared with white patients in the Registry, they were found to be younger, to survive as long, to have less MI and more of the distal intestinal obstruction syndrome. A worrying difference in health service

utilisation was noted. The gastro-intestinal differences were thought to relate to the higher number of compound heterozygotes in the African American group. Nutritional lag was not dependent on CF genotype. This together with the health service data suggested that non-biological factors were impacting detrimentally on the course of CF in African Americans. This was reinforced by a paper in the same edition of the *Journal of Pediatrics* that showed that there was an over-representation of African American CF patients on Medicaid (a proxy for poorer socio-economic conditions).[114]

Of particular relevance to the understanding of CF in SA was the comparison between African American patients homozygous for ΔF508 and those with the ΔF508/3120+1G→A genotype of whom there were 11:

> There were no statistically significant differences between the groups in sex ratio, current age, age at diagnosis, sweat chloride concentration, pulmonary function, percentage of colonisation with *P aeruginosa* and *S aureus* organisms, PS, MI, rate of hospitalization, or frequency of outpatient visits.[111]

Thus, CF in African Americans is not very different from that experienced in Caucasoid populations. Only the higher incidence of some gastrointestinal features could be considered biological (i.e. genetic) in nature. What about CF in non-American Africans? Does the lack of ΔF508 mean a phenotype significantly at variance with that experienced in America may be found in Africa?

Cystic fibrosis in non-American Africans

Cystic fibrosis in non-American Africans has only been described in case reports. Occasional papers have appeared since the 1950s giving clinical details of infants and young children with manifestations suggesting CF. Almost all these children died in infancy.

Two infants were described in the French literature in 1954.[115] These two West African children presented with a syndrome mimicking kwashiokor, a fact of considerable interest to South African CF workers for whom this has a familiar ring.

In a letter to *The Lancet* in 1962, Lorna MacDougall from Toronto in Canada described two Kikuyu children she had seen in Kenya.[116] The first child failed to thrive to the point of emaciation. Pneumonia developed and there was no tryptic activity in duodenal juice. There was some improvement on tetracycline and cow's milk. Mantoux was negative. Stools were pale and bulky. She died during a diarrhoeal illness at 8 months of age. *Post mortem* showed staphylococcal abscesses in the lungs and "typical histological changes of fibrocystic disease" in the pancreas. This was the parents' (both Kikuyu) first child.

The second child described by MacDougall was two years old at presentation. The family background was unknown. He was severely underweight and had bronchiectasis. Mantoux was negative, there was no tryptic activity in duodenal juice even after refeeding, and a Shwachman sweat plate (a screening test of the time) was "strongly positive". Steatorrhoea was present. Follow up was brief.

These two cases are very compatible with CF. As MacDougall pointed out, duodenal enzyme activity is low in malnourished infants but should return with refeeding.

CF was first identified in a South African black child in 1957 and reported by SS Grové, a surgeon in Durban, in 1959.[117] A "Bantu" baby who died within half an hour of birth was found to have intra-abdominal changes suggestive of meconium peritonitis. No mention of the characteristic microcolon of MI was made; indeed, the colon was dilated. However, on histology, glands swollen with mucus were found in the lungs, pancreas and intestines. Reflecting a concern that is to be found in SA writing in the present day Grové wrote,

> Pancreatic fibrocystic disease in the older Bantu child has very likely escaped diagnosis largely because of the fact that many Bantu children suffering from this disease die of an acute respiratory illness either before medical advice is sought or very shortly after, and before clinical investigations have started. Malnutrition, gastrointestinal infections and pulmonary diseases are frequently associated....

Grové hoped that his paper would encourage the identification of CF in "Bantu children". In an addendum, he reported that he had seen another newborn case of CF. Working in SA at the same time, Catzel had been unable to find a case using Shwachman's finger print sweat test on 118 black children.[27] It was to be another 10 years until the next case of CF in a black African from SA was reported.

In 1967 Levin and colleagues at Baragwanath Hospital in Johannesburg described twins born to a Sotho mother and a Zulu father.[118] The first twin presented with intestinal obstruction soon after birth. The X-ray had typical features of MI. At laparotomy there was a perforation of the ileum. The state of the colon was not described. The neonate died not long after surgery. Histology of the bowel showed the typical mucin accumulation of CF in the intestinal glands, appendix and pancreas. Hirschsprung's disease (a more common cause of intestinal obstruction in Africa) was excluded as a cause for the obstruction by the presence of ganglion cells in the colon.

The other twin had loose stools with no tryptic activity from the third day of life. Sweat test using the agar imprinting method of Shwachman was "3+ positive". The child went on to develop oedema, anaemia with reticulocytosis, hypoalbuminaemia and hypopigmentation on the skin. There was an improvement in the child's condition after a blood transfusion and a change to cow's milk formula. Respiratory symptoms developed at 10 weeks of age. Soon chest X-ray changes of consolidation supervened. Further treatment was refused by the family and follow up was lost.

These two cases appear typical of CF - the oedema/anaemia presentation of the second twin being a consistent though uncommon feature of CF - and are compatible with a familial disease. Levin and colleagues noted that a search for other CF patients at Baragwanath Hospital had been fruitless.

Further cases from Francophone Africa were reported in 1981 and 1984. Three children presented with malnutrition in Senegal, being diagnosed *post mortem*.[119] A case report of a Cameroonian child (the same one whose DNA appears in later genetic literature) who travelled to France to have the diagnosis made appeared in 1984.[120] This child called Diana presented with classic CF: severe failure to thrive, steatorrhoea and chest infections. Four sweat tests showed chloride levels above

80mmol/l. Full therapy for CF produced an excellent response and Diana "regagne le Cameroun". The authors claimed this child as the first African child to have CF confirmed with the sweat test.

In his questionnaire-based survey of CF in southern Africa, Super knew of 8 black patients: 5 cases were the ones in the published literature.[28]

The way things stood for CF in South African black populations was summarised by Beighton and Botha in one of the articles they published in 1986, reviewing genetic conditions in SA. In noting its rarity they invoked 'unknown genetic mechanisms" and stated rather oddly that "... knowledge of the rarity of the disorder is important in differential diagnosis and in planning for the provision of health services."[121]

It was not long before molecular genetics was able to bring the final proof that CF was found in Africa. As will be discussed now, molecular genetics was soon claiming that CF among black Africans was by no means as rare as the paucity of case reports over the past 50 years suggested.

A collaborative study of three cases of CF in black South Africans published in 1996 included clinical data and the results of a systematic investigation of the gene for CFTR in each case.[48] All three appeared to have impeccable credentials for no Caucasoid admixture although one father was dead by the time his son was diagnosed with CF. Clinical details were convincing for CF. All three children had repeatedly positive sweat tests. To complete the diagnostic certainty, all 6 chromosomes had CFTR gene mutations on them. Four of them carried the 3120+1G→A mutation that had significant prevalence in African Americans and had not been found in Caucasoids. Another carried a different mutation (G1249E) and the last carried a previously unidentified 54 base pair deletion in exon 17a. Thus there was now unequivocal genetic proof that CF as seen rarely in Africa was a CFTR mutation-based disease. Furthermore the 3120+1G→A mutation was a significant contributor to this (4/6 mutations in this small study) and was likely to contribute significantly to CF in Africa. This finding meant that carriers of this mutation could now be

identified, presenting science with the first opportunity to investigate the incidence of CF in black Africans.

Pursuing the lead given by the prevalence of the 3120+1G→A mutation in African Americans and the new black African cases of CF, Padoa and colleagues from the SAIMR in Johannesburg searched for it and three other mutations that had been found in African Americans (A559T, S1255X, 444delT) in 208 San and 1152 unrelated healthy African black persons from southern, western and central Africa. Their work was published in 1999.[50] Nine heterozygotes, all black Africans and all with 3120+1G→A were found. Statistically it could not be determined if carrier frequencies differed between the chiefdoms studied. Overall, in southern African black groups, eight 3120+1G→A heterozygotes were found out of 728 subjects giving a carrier frequency for this mutations of 1 in 91 (1,1% 95%CI 0,51 – 2,17%).

(Note should be made that one other mutation, D1270N, was found in two symptomatic patients who did not fulfil the criteria for CF. This mutation is rare and usually associated with mild or monosymptomatic CF, usually with normal sweat electrolytes. Its possible role in mitigating the effects of other CF mutations in SA is discussed on p73.)

In the same study the mutations of five new black African CF cases were described. Two chromosomes showed the 3120+1G→A mutation. Combining these five CF cases with the three from the earlier study, 6 out of 16 CF chromosomes (37,5% 95%CI 15,2 – 64,5%) carried this mutation. This meant that the 1 in 91 southern African carriers of the mutation were only 37,5% of the total carrier population. Clearly the wide CIs made estimation of actual carrier frequency very uncertain: anywhere from 1 in 14 to 1 in 59. However what was most important about these carrier frequencies was that they encompassed the rates for both the South African white and coloured populations. This study suggested that *CF among South African blacks should be seen as often as in the known CF-carrying populations of the country!* Using 1994/5 birth figures, Padoa and colleagues estimated that between 57 and 1015 black African babies are born with CF every year in SA, or an incidence of between 1 in 796 and 1 in 13 964.

South African clinicians and scientists are faced with a challenge: to find the missing black CF cases or to explain why they are not being diagnosed. The following section uses case reports from the RCCH to pursue this issue.

STUDY 3.3 WESTERN CAPE EXPERIENCE WITH CYSTIC FIBROSIS IN BLACK PATIENTS

Five black African cases of CF have been diagnosed at the RCCH since 1984. They each illustrate the evolution of our understanding of the disease in this 'group'.

CASE 1 "Cystic fibrosis unlikely because of race." 1984

This child of a Xhosa-speaking mother was born prematurely in 1983. She presented at two months of age with a macrocytic anaemia and was failing to gain weight. She was hypoproteinaemic and had a lower respiratory tract infection with lower airways obstruction. She was investigated for the anaemia with genetic haematological causes being ruled out. A blood transfusion was given. Weight gain in the ward was very poor and the respiratory infection persisted. *Haemophilus influenzae* was grown from sputum. Gastro-oesophageal reflux (GOR) was demonstrated. After discharge she was readmitted a month later with another chest infection and dehydration. The diagnosis of 'early kwashiorkor' was also made. GOR was thought to be a significant factor in her chest disease although a pH study was negative. In view of persistent poor weight gain and chest signs a sweat test was performed (Table 3.12). As it was abnormal it was repeated. Tests for malabsorption were undertaken: fat globules were seen, tryptic activity was normal, faecal fat testing was unsuccessful. The gastroenterology team was called in who felt that the child's 'race' made CF unlikely. Endocrine testing was then undertaken and proved to be normal. The child stayed in hospital for six months, gaining some weight on an elemental formula. By the time of discharge, five positive sweat tests had been obtained. After a 6^{th} positive test, the CF Clinic followed the child but felt unwilling to attach a definitive CF diagnosis to the child. A 7^{th} and an 8^{th} sweat test were positive. The child, now aged two and a half years, presented with a severe lower respiratory chest infection soon after this and rapidly succumbed. *Post mortem* demonstrated a severe *Pseudomonas* pneumonia with air trapping. There were typical changes of CF in the pancreas.

Table 3.12 Sweat tests results for Case 1

Sweat sodium (mmol/l)	Sweat chloride (mmol/l)	Sweat mass (mg)
82	134	
67	108	
83	122	157
68	101	
73	96	280
73	102	386
78	110	427
95	131	206

This child never received a positive diagnosis of CF and thus could not benefit from definitive treatment. The diagnosis was proven by *post mortem* but never taken further either by way of family studies or by way of education for SA's child health practitioners. Case 2 could not benefit from the experience with Case 1.

CASE 2. "Do a sweat test." 1993

This child presented in 1993 at three months of age to TBH with pneumonia and failure to gain weight. His mother was Xhosa-speaking and he was her fourth child. His father, said to be from the same group but not the father of the other three children, had been murdered. TB was suspected and, after investigation, follow up was arranged. The child was soon ill again and presented to the RCCH with a collapsed right middle and left lower lobes and severe air trapping. There was some response to broad spectrum antibiotics but severe lower airways obstruction persisted. A pulmonologist was called in who, amongst other tests, requested a sweat test. The ward staff viewed this suggestion with incredulity but went ahead. The result was positive (Test 1: mass 77mg Sodium 78mmol/l, Chloride 114mmol/l) as was a second test (Test 2: mass 153mg Sodium 94mmol/l, Chloride 104mmol/l). Because he was a black African child a third test, which also proved positive (Test 3: mass 299mg Sodium 83mmol/l, Chloride 103mmol/l), was performed. By now molecular testing was available and being pursued vigorously by the Department of Genetics at the University of the Witwatersrand. With the help of colleagues in France, they were able to demonstrate two CF mutations. One was the 'African mutation', 3120+1G→A, and the other was a unique mutation, 3196del54.[49] This child has

shown a typical course of CF with PI, and *S aureus* and mucoid *P aeruginosa* in the chest. He is 11 years old at the time of writing.

Experience with this case coincided with new knowledge about CF mutations in black South Africans. Case 3 now benefited from the RCCH's experience with CF in the Xhosa-speaking population and the new diagnostic modality.

CASE 3. Not HIV, so what is cause of the problem? 1995

This infant was born in Kingwilliamstown to Xhosa-speaking parents who were both professionals. He had not grown since birth and was severely wasted. He had persistent changes on his chest X-ray with marked air trapping. He had a firm hepatomegaly. He had been admitted to Livingstone Hospital in Port Elizabeth where he had been investigated for TB and HIV infection repeatedly with negative results. He was transferred to RCCH for further testing. CF seemed likely despite the child's 'race' and was proven within a few days: 2 sweat tests were positive (Test 1: mass 371mg Sodium 80mmol/l, Chloride 107mmol/l: Test 2: mass 356mg Sodium 82mmol/l, Chloride 99mmol/l), there was a high faecal fat level and mucoid *P aeruginosa* and *S aureus* were grown from the sputum. Full treatment for CF was commenced and, once the child was stable, he was transferred home to have paediatric follow up in Kingwilliamstown by a paediatrician from Cecilia Makiwane Hospital in East London. Unfortunately, despite this plan, the child was lost to follow up.

This case, following hard on the heels of Case 2, was rapidly diagnosed at the RCCH. His diagnosis brought the message of CF occurring in black African children to paediatricians in the Eastern Cape province.

CASE 4. Atypical case in atypical race. 2001

This male child of Xhosa-speaking parents presented at two years of age with repeated pneumonia and failure to thrive from the age of 9 months. Investigations for TB had been negative and the family were not poor. He had had diarrhoea intermittently from infancy. There was no family history suggestive of CF. On admission he had lung hyperinflation and respiratory distress. Chest X-ray confirmed air trapping and there were changes in the right upper lobe and perihilar regions.

53mmol/l, Chloride 45mmol/l). Tests for fat malabsorption were unsuccessful. Mutation analysis covering common South African mutations including 3120+1G→A was negative. CF was thought probable but not proven. With a respiratory infection two months later mucoid *P aeruginosa* was grown from his sputum, increasing the likelihood of CF. He was treated with PERT, nutritional advice and support and physiotherapy. Follow up was fitful despite appointments being given. A year later, during which time he had had a few mild respiratory infections and had gained weight, a fourth sweat test was again equivocal (Test 4: Mass 265mg, Sodium 56mmol/l, Chloride 55mmol/l). His X-ray showed persistent air trapping and perihilar infiltrates. He is now 4 years old and stable on his therapy. His asymptomatic seven year old sister also had an equivocal sweat test result (Mass 186mg, Sodium 70mmol/l, Chloride 54mmol/l).

With this patient CF among black Africans had joined the mainstream at the RCCH: recurrent chest infections leading to an investigation of CF and a complex of suggestive symptoms and test results but no absolute proof. 'Race' was no longer a factor against the diagnosis. The case also illustrated the need for greater investigation of CFTR mutations and variations among black Africans. Is CF perhaps phenotypically different in Africa?

CASE 5. Typical presentation in infancy; instant diagnosis. 2003

This male infant of Xhosa-speaking parents presented at the age of two months with dehydration and diarrhoea. There were no chest signs or symptoms and no significant family history. Investigation revealed a hypochloraemic metabolic alkalosis. Sweat tests were ordered by junior doctors in the Rehydration Unit and the diagnosis of CF confirmed. Mutation analysis showed the child to be a compound heterozygote with one copy of the 3120+1G→A mutation.

This encouraging case illustrates that CF is part of the differential diagnosis of children presenting with suggestive features in contemporary Cape Town. The challenge presented 20 years ago when Case 1 was born has now largely been met: CF occurs in black Africans and is being considered in clinical situations by non-experts.

Dr George du Toit and I described a case in whom the diagnosis of CF was strongly entertained but never proven in the *South African Respiratory Journal* in 2001.[122] This black African child had short stature, intermittently positive sweat tests and severe resistant peripheral airways obstruction early in life with no typical CF pathogens but no pancreatic disease and no identifiable mutation. We aimed to illustrate issues around diagnosing CF and to discuss the apparent discrepancy between the paucity of proven cases of CF in black South Africans and the expected incidence based on the carrier rate calculated by Padoa and colleagues.[50] As illustrated by the case reports above, awareness has risen greatly at the RCCH and its associated services. Many other children with suggestive presentations including the anaemia/oedema complex have had sweat tests. Despite this, only three cases in black Africans in the Western Cape have been proven since then. One of those (Case 4) was atypical.

Where have all the black cystic fibrosis patients gone?

Padoa and colleagues predicted that at least 57 black African babies with CF would be born each year in SA.[50] The number diagnosed in recent years countrywide does not reach double figures (Personal communication – members of the MSAC to the South African CF Association). There are three potential explanations for this discrepancy between actual and predicted cases of CF among black Africans in SA.

Firstly the data presented by Padoa and colleagues[50] may not represent the truth i.e. there was a sampling bias or too much statistical uncertainty. Healthy unrelated subjects were drawn from specimens in the Johannesburg laboratory. Such population based samples are unlikely to contain biases that select for CF carriers. It is noticeable that no carriers of the 3120+1G→A mutation were found in the Nguni language groups. While this was not statistically different from other groups, the sample size may mask a difference that a larger sample base might have revealed. For example, only 52 healthy Xhosa subjects were tested for the 3120+1G→A mutation; no carriers were found (95% CI 0 to 1 in 16). A sample size of 200 in which no carriers of the 3120+1G→A mutation were found would still have an upper CI equal to the carrier rate for all mutations in the coloured group (1 in 55). Thus, to prove that CF is *not* significantly common in this group would take a large and laborious study.

carriers of the 3120+1G→A mutation were found would still have an upper CI equal to the carrier rate for all mutations in the coloured group (1 in 55). Thus, to prove that CF is *not* significantly common in this group would take a large and laborious study.

Is it possible therefore that the Sotho chiefdoms (not including the Tswanas in whom no carriers were found) are the only group to have significant CF carrier rates (1 in 42 95% CI 1 in 20 to 1 in 114)? Much of this group lives in poorer areas of SA such as the Free State, Mpumalanga and Limpopo provinces where infant mortalities are high and health services may not recognise the disease. In the Western Cape province the Xhosa chiefdom is the dominant black African group. Does this explain the paucity of CF patients in this area? Perhaps the lack of CF cases in a medically sophisticated and aware region such as the Cape Metropole indicates the true state of things and warns us against searching beyond phenotypically suspicious cases for CF in black Africans in this region. Likewise KwaZulu Natal province, dominated by the Zulu group might have a very low carrier rate. Indeed according to 2001 Census data, isiXhosa and isiZulu speakers account for over half of all African language speakers in SA.[123] The province of Gauteng with its mixed population and good health services may be only part of the country where the black CF patients are likely to be found in significant numbers. The number of new patients there seems to be rising.[124] Perhaps there is less reason for assiduous searching for 'missing' cases in areas where Sotho groups are a small minority?

A second reason for the discrepancy between predicted and diagnosed black African CF patients was discussed in Padoa and colleagues' paper[50]: high infant mortality, low awareness of CF and poor health service infrastructure in much of SA. If one assumes that the overall carrier frequency calculated by Padoa and colleagues applies equally across all chiefdoms, then about 4 black African children with CF should be born in the Western Cape province every year. In fact fewer than one is diagnosed per year in the Western Cape province which has relatively sophisticated health services. Most children with severe ongoing health problems reach the health services. (Many patients arrive from other provinces because of this fact.) Severe failure to thrive, chronic and progressive lung disease, neonatal intestinal obstruction: all these manifestations of CF, if found in a child in the Western Cape province, are very likely to reach an expert in children's health. As demonstrated above, CF is

being considered in black African children with symptoms of the disease in the Western Cape province making such large scale under-diagnosis in this area unlikely.

Thirdly it is possible that CF is a milder or phenotypically different disease in South African black persons. If one allowed the hypothesis that health services were missing most cases of CF owing to ignorance and the poverty of many patients, those neonatal CF patients with MI should still get through the system to a paediatrician or surgeon. They are not being seen. Is this because the MI phenotype occurs less frequently that the 15% reported elsewhere? Of the 12 non-black African CF patients who had at least one copy of the 3120+1G→A mutation, 2 had MI: a normal ratio for a 'severe' mutation.

The two atypical cases described above may lend support to the possibility that CF is different phenotypically. However, the common 3120+1G→A mutation, when seen in African American black patients and in the few homozygotes (both coloured and black African patients) we have treated, has been associated with typical and severe CF. It is possible that there is a high incidence of genes that mitigate the effects of this mutation in SA's black patients. Alternatively the significant proportion of unknown CF mutations in this population may be associated with milder disease in some cases. There is as yet no proof of this hypothesis, but there is one tantalising scrap of evidence. In their mutation analysis of the nine patients with symptoms suggestive of CF, Padoa and colleagues' describe two patients who were heterozygous for the D1270N mutation.[50] One of these had a negative sweat test and the other had not been tested. The first of these patients, a male child, was seen at the RCCH at the age of 9 years with bronchiectasis and lower airways obstruction of unknown aetiology and which appeared not to be progressive or to be very slow in progression. No pathogens were grown from his sputum. He was well grown and had no features that suggested PI. Two sweat tests were negative. The D1270N mutation is associated with very mild CF, particularly congenital bilateral absence of the vas deferens.[125] Sweat tests are often normal. Padoa and colleagues did not screen their healthy subjects for this mutation yet 2 of 9 symptomatic subjects had one copy of it. Is it possible that this mutation is playing a role in modifying CF in black African subjects, lowering sweat electrolyte levels and mitigating PI and the progression of CF lung disease? [It should be noted that in the Discussion section of their paper,

Padoa and colleagues muddy the water somewhat by stating that, contrary to what is presented in the Results section, the two patients also had the 3120+1G→A mutation and positive sweat tests. As our Cape Town patient did not have either, this is presumably a mistake.]

Presently there is not enough firm evidence to give credence to any one of these three possible explanations of the lack of black African CF patients in SA. Certainly it would be unfortunate if there were significant numbers of children with typical CF who were not receiving therapy that would allow them to live productive and relatively healthy lives. Efforts to raise CF awareness amongst health workers should continue. It may also be useful to apply sweat testing and mutation analysis to black African patients (both adults and children) with chronic respiratory and GIT symptoms for which no cause has been found. Testing such patients for the 3120+1G→A and the D1270N mutations could be undertaken to explore the place of these mutations in lung and gastrointestinal disease. A larger screening for carriers in the healthy persons from the Xhosa and Zulu chiefdoms is probably not justified. The aim must be to identify and treat symptomatic patients who have classic CF or a possible African variant.

CHAPTER 4

GENERAL CLINICAL ASPECTS

OUTLINE OF CHAPTER

This chapter details the clinical aspects of CF as seen in this CF population in two ways: the presenting symptoms including time to diagnosis, and the clinical features. Both aspects are put into the context of CF as seen in other countries.

BACKGROUND AND LITERATURE REVIEW

As discussed in Chapter 1, the basis of CF as a clinical entity is, in large part, due to the effect of mutations in the gene coding for a CFTR-linked chloride channel. This channel is found at the apex of certain cells of exocrine glands. Many organs have exocrine functions and thus CF is a multisystem disease. The bulk of typical symptoms and signs relates to the pancreas and lung but, as described in the introduction to this work (Chapter 1), the genital tract, intestine, liver, upper respiratory tract and skin may all be directly affected by abnormalities of CFTR function. On top of these direct effects, secondary effects on skin, bones and joints, blood and the endocrine system are not uncommon. If complications of the management of these organ-based effects of CFTR dysfunction are added to the clinical spectrum of disease, the range of disease associated with CF is vast and complex.

This chapter will discuss two related clinical aspects of the pattern of CF seen in the Western Cape province: clinical features at the time of diagnosis ("presentation"), and clinical features encountered during the lives of the patients cared for at the RCCH. Other clinical aspects of the disease are explored in Chapters 5 (Surgery), 6 (Nutrition and Growth) and 7 (Lung disease).

Despite its single gene origins, the clinical course of CF is highly variable. The disease may vary from single organ involvement to a constellation of organ disease developing at any time through a life with CF. Whether and when a particular manifestation of the disease will occur and how rapidly it will worsen is in large part highly unpredictable. Even one of the commonest features of CF such as pancreatic insufficiency (PI) may develop any time in a patient's life.

Factors known to influence the manifestations of the disease in the individual include CFTR genotype, other genes, delay in diagnosis, environmental and health service factors. Exactly how these and other unknown factors influence the course of the disease in an individual patient is often not known. Siblings can have different manifestations and severity of disease.

PART ONE: PRESENTING FEATURES OF CYSTIC FIBROSIS

The classical picture of untreated CF is of an infant who fails to gain weight despite possessing a voracious appetite, passes voluminous malodorous stools and coughs continuously. This is the type of patient described in the 1930s by Fanconi.[1] An infant with this triad of symptoms almost certainly has CF. Singly each of these three typical symptoms, which in organ terms relate to the pancreas and lung, may also be the initial manifestation of the disease. The lower respiratory CF disease, which is the commonest marker of CF disease, can manifest with symptoms such as the persistent pertussis-like cough seen in infancy, recurrent chest infections (often with atypical organisms such as *Pseudomonas aeruginosa* if microbiological tests are done) and persistent chest problems. An acute severe bronchiolitis-like illness is also a well recognised initial manifestation of CF.[126] In time the signs of chronic obstructive and suppurative pulmonary disease will be evident on examination. The pancreatic disease usually manifests as poor growth and chronic steatorrhoea or non-dehydrating diarrhoea. In combination with these lower respiratory and pancreatic manifestations or singly, other organ disease may produce symptoms or signs that point to the presence of CF.

The earliest of all the manifestations of CF is meconium ileus (MI) which is due to CF-related intestinal disease. This may be suspected antenatally (or recognised if there is family history of CF) by ultrasound when bowel obstruction with or without meconium peritonitis is seen.[127] Soon after birth, a child with MI will show signs of intestinal obstruction. Rectal prolapse is another not uncommon presenting feature of CF. The presence of rectal prolapse in a child should lead to serious consideration of CF as the cause.[128] It results from chronic steatorrhoea and loss of anal tone and muscle bulk as a result of the nutritional deficits associated with untreated CF. Also owing to intestinal disease, but much less common than MI and rectal prolapse, are intestinal symptoms later in life. Occasionally appendiceal disease develops owing to inspissated secretions that block the orifice of the appendix, leading to an appendix mass or appendicitis.[129] Appendiceal histology shows the accumulation of mucus, leading to the diagnosis of CF.

The characteristic high electrolyte levels in sweat results from an inability of eccrine sweat glands to resorb chloride ions. This excessive loss of chloride and sodium can lead to another of the presenting features of CF, a hypochloraemic metabolic alkalosis.[130] The saltiness of the sweat has alerted some parents to the presence of CF in their offspring. The upper respiratory tract features associated with CF are nasal polyposis and obstructive upper respiratory tract symptoms and these may be presenting features of the disease. Hepatobiliary manifestations of CF may be the clue to its presence. In early life liver involvement may show itself as a neonatal hepatitis-like syndrome with cholestasis.[131] Later in life, and less commonly, hepatic cirrhosis may occur but this is very seldom the only feature of CF when the disease is recognised. A secondary effect of pancreatic and intestinal malabsorption early in the life of a child with CF is hypoproteinaemia associated with multiple nutritional deficiencies.[132] This manifests as a variable combination of growth failure (due to fat malabsorption), oedema (due to hypoproteinaemia secondary to protein malabsorption), skin rash (due to vitamin and mineral deficiencies) and anaemia (due to protein and vitamin E deficiencies) - the 'anaemia/oedema complex' presentation.

Later in life male infertility due to involution of the vas deferens may be what alerts clinicians to the diagnosis.[133] Recurrent pancreatitis is now recognised as another 'late' presentation of CF.[134]

Two non-symptomatic reasons for the diagnosis of CF being made result from screening for the disease either as part of a neonatal screening programme or because of a family history of CF ('cascade screening'). Another means of making a non-symptomatic diagnosis is by antenatal genotyping through amniocentesis or chorionic villus sampling.

An analysis of the mode of presentation of CF in a particular population can be helpful in giving pointers to improving the early diagnosis of the disease in a population or geographical area. The frequency of typical versus less typical presentations can inform educational goals for health workers. Atypical presentations may have particular relevance for certain populations. In Saudi Arabia, for example, neonatal cholestasis as a presenting feature of CF is unusually common.[135] Clinical features of CF and patients' age at diagnosis can indicate whether diagnostic delay is a problem and in what way. Delays in attention to nutrition and management of respiratory disease have the potential to worsen the prognosis in an individual with CF so the aim must be, in the absence of population screening, to have CF diagnosed clinically as early as possible. Gender has been found to influence prognosis in CF. Delay in the diagnosis of CF in girls may be a factor in this 'gender gap'.[136 137]

The frequencies of the various modes of presentation in the USA have been reported from the Cystic Fibrosis Foundation (CFF) National Patient Registry and give a clear picture of the typical pattern in a Western country. These are shown for 20 096 CF patients in August 1997 in Table 4.1.[60]

Table 4.1 Presenting features of 20 096 patients reported to the Cystic Fibrosis Foundation (USA) National Patient Registry (adapted from Ref. 60)

	Percent*
Acute or persistent respiratory symptoms	50,5
Failure to thrive/malnutrition	42,9
Steatorrhoea/abnormal stools	35,0
Meconium ileus/intestinal obstruction	18,8
Family history	16,8
Electrolyte imbalance	5,4
Rectal prolapse	3,4
Neonatal screening	2,3
Nasal polyps/sinus disease	2,0
Genotype	1,2
Hepatobiliary disease	0,9
Prenatal diagnosis	0,8
Other	1,2
Unknown	1,9

*Not mutually exclusive

As discussed in Chapter 3, patients with CF in the Western Cape province are uniquely genetically diverse. Is this reflected in their presentation? We suggested in a letter to the *SAMJ* in 1996 that the anaemia/oedema complex presentation of CF presented particular diagnostic challenges in SA.[138] How common is this presentation in SA context? SA is also historically unique. Does ethnic group both in its 'racial' implications and in its capacity as surrogate for socio-economic status in SA under apartheid and beyond influence the age of recognition of CF? These considerations will also impinge on the analysis of the prognosis of CF in SA (Chapter 9).

As the recognised clinical spectrum of CF has expanded more atypical cases have been identified later in life. Is this the case in SA?

Apart from our *SAMJ* letter,[138] the presentation of CF in SA has been discussed in two papers. Hill and colleagues' from Cape Town in 1988 outlined the presentation in 106 patients.[33] Respiratory symptoms dominated. Poor growth was the second most common feature. The classic triad of recurrent chest disease, diarrhoea or steatorrhoea and failure to thrive was very unusual, being seen in only two cases. A 1984 report on adolescent

and adult patients from Johannesburg only reported respiratory and gastrointestinal (which included 'weight loss') presentations or a combination of the two.[32] Respiratory presentations dominated (50%).

In Hill and colleagues' study all 106 patients had been diagnosed by 12 years of age.[33] The mean age at diagnosis was 20,6 months. Nearly three quarters of the patients had been identified by five years of age. This study came from a children's hospital though it included adults with CF. In the 1984 Johannesburg study, only 6% of adolescent and adult patients had been diagnosed in the teenage years or beyond indicating that almost all diagnoses in the 1960s and 1970s had taken place during the childhood years.[32] In a similar figure to that in Cape Town (which covered a similar period but extended further in to the 1980s), almost 70% had been identified by five years of age. That there was a need for improvement at age of diagnosis of CF in the 1980s was indicated by Hill and colleagues' finding that the mean age of onset of symptoms was 16 months before the mean age at which the diagnosis was made (4,2 months versus 20,6 months). Furthermore, whereas 95% of patients had been symptomatic by one year of age, only 63% had been diagnosed as having CF during infancy.

In order to answer some of the questions posed above and to describe the situation regarding the presentation of CF in SA in recent decades, a study of this issue in the Western Cape province was undertaken.

STUDY 4.1 Presenting features of cystic fibrosis in the Western Cape province

Study objectives

1) To determine the presenting features of CF in the Western Cape province
2) To determine the age at diagnosis of CF in the Western Cape province
3) To determine whether gender, ethnic group or year of birth influence the time to diagnosis of CF

Study population

The 181 CF patients described in Chapter 2.

Study Methods

Data

The following data were extracted from the patients' hospital folders:

1) Demographic features
2) Age at diagnosis
3) Year of birth.
4) Clinical features at diagnosis. These features were recorded in two forms: individually and in groups. Features were assessed through the record of symptoms ('history'), signs of organ involvement ('clinical examination') and results of clinical tests at presentation ('investigations'). Routine screening tests for organ involvement were not part of clinical assessment of new cases. The groups of features were classified as: Gastrointestinal tract (GIT) only (excluding MI), MI only, Chest only, Other single feature, Classic triad (steatorrhoea, recurrent or persistent chest symptoms and growth failure/malnutrition), Other combination.

Data analysis

Basic statistical analysis of the data included absolute numbers and frequencies. Gender and ethnic group data were compared using Chi^2 statistics with Yates' correction where groups had fewer than 5 cases. For analysis of potential changes in time to diagnosis over the period under study, children born in two decades

were compared (1975 – 1984 [Period 1] and 1985 – 1994 [Period 2]). Since there are only 9 years from the end of Period 2 to the end of the study period, only children diagnosed by the age of 9 years were included in this analysis. Age-related data for groups were compared using non-parametric statistics.

Results

Presenting features of CF were recorded in the notes in all but 7 (3,9%) cases. These 7 cases had been referred with established CF from other centres. The number of patients with each of 15 individual presenting features of CF in the remaining 174 patients are shown in Table 4.2. Lower respiratory tract features were present at diagnosis in 121 patients, 69,5% of the total. The presence of *P aeruginosa* in acute pneumonia led to a diagnosis of CF in 4 cases. Four other patients were diagnosed as having CF while on ventilatory support for acute lower respiratory tract infections.

In 15 of the 18 patients with a family history, a sibling was affected with or had died of CF. One younger sibling of a known CF case had had MI diagnosed through antenatal ultrasound screening. Three families who had had a child (one family had had two) who had died of a condition that was probably CF before the index case was diagnosed were not included under Family History in Table 4.2.

Table 4.2 Individual presenting features of cystic fibrosis

Presenting Feature	Number	Percentage of patients with feature*
Failure to thrive/malnutrition	49	28.2
Recurrent chest infections	40	23.0
Steatorrhoea/abnormal stools	35	20.1
Meconium ileus[$]	28	16.1
Acute or atypical pneumonia	23	13.2
Family history	18	10.3
Persistent chest symptoms	16	9.2
Rectal prolapse	11	6.3
Anaemia/oedema complex	10	5.7
Chronic obstructive airways disease	7	4.0
Electrolyte imbalance	6	3.4
Hepatobiliary disease	3	1.7
Nasal/sinus disease	3	1.7
Salty taste	2	1.1
Appendix histology	1	0.6

*Total patients = 174
[$] One patient had the meconium plug syndrome

No patients were diagnosed through newborn screening. Likewise, although prenatal genetic diagnosis has been made in Cape Town, this has always been in the context of abortion of the affected fetus.

None of the 3 cases in which there was hepatobiliary disease at presentation had infantile cholestasis and in none of them was the liver disease the principal reason for suspecting CF.

Analysis of presentation by groups of features of CF at the time of diagnosis is shown in Table 4.3. The 'Other single feature' group was made up of family history (12), anaemia/oedema complex (6), failure to thrive (4), electrolyte imbalance (3), and nasal polyposis (1).

Table 4.3 Groups of features of CF in patients at the time of diagnosis

Group	Number* (%)
Chest only	45 (25,9)
Meconium ileus only	25 (14,4)
Gastrointestinal only	18 (10,3)
Other single feature	26 (14,9)
Classic triad[$]	8 (4,6)
Other combination	52 (29,9)

*Total = 174
[$]Steatorrhoea, recurrent or persistent chest symptoms, growth failure/malnutrition

In terms of groups of features of CF, no statistical differences in presentation between two main ethnic groups could be identified except in the case of pure gastrointestinal presentations (excluding MI) (Table 4.4). There was no difference between coloured and white patients in terms of having malnutrition at the time of presentation ($Chi^2 = 1,27$, $p = 0,25$). Of the 28 children who presented with MI, 18 were white and 10 were coloured (no statistical difference $p = 0,33$). However the anaemia/oedema complex was present at diagnosis in 8 coloured children versus only one white child (the 10th child was black African – Case 1 p67). This difference was statistically significant ($p = 0,005$). The single white child was 12 months of age when the diagnosis was made whereas all the other children had the diagnosis made by 6 months of age.

Table 4.4 Groups of features of cystic fibrosis in patients at the time of diagnosis: ethnic group

Group	Number* (%)		Chi^2
	Coloured (N = 51)	White (N = 71)	
Chest only	21 (41,2)	23 (32,4)	0,99 (p = 0,32)
Gastrointestinal only	3 (5,9)	15 (21,1)	5,48 (p = 0,02)
Classic Triad[$]	5 (9,8)	3 (4,2)	0,73 (p = 0,39)
Other combination	22 (43,1)	30 (42,3)	0,01 (p = 0,92)

*Total = 122 (Patients with meconium ileus alone were excluded from this analysis)
[$]Steatorrhoea, recurrent or persistent chest symptoms, growth failure/malnutrition

The overall mean age at diagnosis was 22 months. The median age was 6 months (range 0 – 169 months, interquartile range 3 – 30 months). The ages at diagnosis did not differ

for the white and coloured groups (p = 0,67, Mann-Whitney U test). The proportion of patients diagnosed in infancy was 58,9%.

The median age at diagnosis of those without MI was 12 months. If those diagnosed in infancy who, at birth, had an older sibling known to have or to have had CF are also excluded from the analysis (where the family history, as with MI, led to an early diagnosis), the median age at diagnosis of this CF population (N= 148) was 14,5 months. The median age at diagnosis for females in this group was 9,5 months and for males 19 months. This difference just achieved statistical significance (p = 0,05, Mann-Whitney U test). The median ages at diagnosis for the two largest ethnic groups (again excluding cases with MI and/or older siblings with CF) were: white 15 months (range 1 – 137 months), coloured 9 months (range 2 – 169 months). There was no statistical difference between these groups (p = 0,186, Mann-Whitney U test).

The presenting complaints of the 21 (11,6%) patients who had not been diagnosed by their 5th birthdays are given in Table 4.5. The three patients with a family history (Patients 80, 63 and 86 Appendix A) were diagnosed when a younger sibling was shown to have CF. Eight of the 21 patients were PS at diagnosis (including the three siblings). Only one of the 9 children diagnosed after the age of 7 years was female.

Table 4.5 Presenting features of patients diagnosed after their 5th birthdays

Patient number*	Age at diagnosis (years)	Gender	Ethnic group	Clinical features
34	5.2	M	C	Persistent chest symptoms, hepatomegaly
64	5.5	F	W	Steatorrhoea
61	5.6	F	C	Chronic lung disease
13	5.7	M	C	Recurrent chest infections, steatorrhoea
8	5.9	F	W	Recurrent chest infections
94	5.9	F	C	Chronic chest symptoms, FTT, steatorrhoea
87	6.0	M	W	Persistent chest symptoms, underweight
80	6.0	F	C	Sibling
102	6.6	F	W	*Pseudomonas* pneumonia, bronchiectasis
140	7.5	M	C	Bronchiectasis
23	7.7	M	W	Steatorrhoea
110	7.9	M	W	Recurrent chest infections
33	7.9	F	W	Pneumonia
63	8.0	M	C	Sibling
121	9.3	M	W	Recurrent bronchitis
86	9.3	M	W	Sibling
97	9.7	M	W	Recurrent chest infections
3	10.0	M	W	Steatorrhoea, persistent chest symptoms
49	10.8	M	W	Recurrent chest infections
74	11.4	M	W	Nasal polyposis
32	14.1	M	C	Chronic lung disease, liver cirrhosis

* see Appendix A
M = Male, F = Female
C = coloured, W = white
FTT = Failure to thrive

Sixty seven patients were born in Period 1 and 59 in Period 2. The median (mean) ages at diagnosis for the two periods were 8 (21) months and 10 (19,5) months respectively. There was no statistical difference between the periods (p = 0.63 Mann-Whitney U test). Omitting cases with MI and an older sibling with CF, the figures for the two periods (Period 1 = 51 patients, Period 2 = 52 patients) changed to 18 (27) and 11,5 (22) months but were still not significantly different (p = 0,44 Mann-Whitney U test).

Discussion

The diagnosis of CF depends on the recognition by a child's family and health workers of symptoms and signs that suggest the disease. Most South African families will not have heard of CF since it does not have the public profile it has in countries with predominantly Caucasoid populations. Family history of the disease is unusual as CF is an autosomal recessive condition, and, even where there is a family history, except in the case of siblings, that history is only thought of after the diagnosis is made. One in ten children had a family history of CF in this study. In nearly all cases it was a sibling. A more distant relative with CF was rare, confirming that the absence of a family history of CF is the norm in Cape Town as it is elsewhere.

As shown by Hill and colleagues[33] and confirmed here, the classic triad of presenting features of CF is unusual in Cape Town. Indeed only one third of our cases had recognised malnutrition at diagnosis (failure to thrive 49, anaemia/oedema complex 10 = 59/181). Malnutrition gains greater status as a presenting feature of CF if the cases who presented with MI or had an older sibling with CF (and thus had a very early diagnosis) are excluded but, even so, fewer than half the cases (59/148) were recognised as malnourished at diagnosis.

That malnutrition is significant at diagnosis of CF has been demonstrated by the Wisconsin controlled study of screening for CF.[139] Length, weight and head circumference were all significantly lower in the unscreened population when the diagnosis was made. It is likely that the same nutritional deficits pertain in SA. The North American Registry study which was less rigorous as it depended on clinical assessment by staff at CF Centres throughout the USA, gave a figure for the prevalence of malnutrition at diagnosis of 35,6%,[140] in keeping with that reported here. In this study the presence of malnutrition was not gauged by detailed anthropometrics or blood investigations; it depended on clinician's notes and their assessment of basic data such as weight and, less often, length or height. It has been our experience that many newly diagnosed children with CF rapidly gain weight after the initiation of pancreatic enzyme replacement therapy (PERT) and dietary therapy even when their weights fall within the

'normal' range at diagnosis. This early catch up growth was also demonstrated in the Wisconsin trial.[139] Importantly, the finding that fewer than half of the children had features of malnutrition on straightforward clinical assessment means that South African clinicians who expect this to be present in order to suspect CF are going to miss the diagnosis.

Lung disease affected two thirds of patients, making it more important than malnutrition as a clue to the presence of CF. Indeed chest disease alone was the presenting feature in a quarter of the cases. This study demonstrates that, in SA, a wide variety of respiratory presentations can be presenting features of CF. While 'recurrent chest infections' are well known as a reason to think of CF, 'persistent chest symptoms', meaning that the child is not particularly sick but always coughing or productive of sputum, is also a significant respiratory presentation. Asthma is a much more common cause of this symptom complex but CF should be considered if there is an inadequate response to asthma therapy or if there is associated malnutrition. Likewise the association of severe acute lower respiratory tract disease and early presentation of CF is less known than it should be given that 4 children were on ventilators before CF was thought of. As shown as long ago as 1974, CF may need to be considered in any infant with an acute life-threatening lower respiratory tract infection characterised by marked lower airways obstruction.[126]

While abnormal stools must have been present in those with malnutrition (as lung disease of sufficient severity to cause growth disturbance is unlikely in CF without PI), they had often not been recognised as abnormal by the family. Thus health workers need to think of CF in children with unexplained malnutrition and persistent chest disease alone as well as in combination, even if there are no apparent GIT symptoms.

The anaemia/oedema complex presentation affected about one in 20 children. Two of the 10 cases were diagnosed *post mortem*. All those diagnosed while alive had been diagnosed since 1988 suggesting that there was lack of awareness of this presentation in the earlier years. The first child to be diagnosed with this presentation *ante mortem* spent

two months in hospital being investigated for anaemia before CF was considered. He died soon after the diagnosis was made. A similar case dominated by anaemia in which vitamin E deficiency played a major part has been reported from Detroit in the USA.[141] The younger sibling of our patient presented similarly four years later and the diagnosis of CF was rapidly proved. Based on this study, at least one child with CF presents in this fashion every 18 months or so in Cape Town. As we noted in 1996, children with this form of CF may even now be dying labelled as having kwashiorkor.[138] Phillips and colleagues presented two cases in the UK who had features that mimicked kwashiorkor,[132] so how much more will confusion occur in SA where the malnutrition syndrome remains prevalent? Interestingly, this presentation and its pitfalls in poor societies has been recognised in South Asia.[142] Is this lack of recognition of this presentation of CF the reason that some of the black African children with CF are 'missing'? Of note is the early age at which features of anaemia/oedema develop (less than 6 months in all but one case). This is consistent with the literature on CF but is earlier than the age that nutritional kwashiorkor develops which is typically in the second year of life. The late diagnosis of the one white child to have this syndrome, the daughter of parents from the professional classes, demonstrates the lack of recognition of this syndrome in SA.

The first study to estimate the proportion of patients with CF who present with oedema was published in 1978.[143] This paper noted the case reports of this presentation that stretch back to the 1940s though only those from the 1960s forward were reviewed in the paper. Writing from Montreal, Canada, the authors reported 6 cases (2,6%) out of the 229 identified as having CF over a 10 year period. This is just over half the Cape Town incidence reported here. Reporting three years later, Danish authors described 7 out of 130 infants (5,4%, 95% CI 2,17-10,84%) who had presented under the age of 6 months and who turned out to have CF.[144] While this seems to be a higher incidence than the Montreal study, the denominator was different as it only contained infants. It is not possible to compare these data with Cape Town's since the age of diagnosis of some children in the Danish series does not coincide with their presentation with anaemia/oedema. Abman and colleagues from Denver in the USA reported that 13%

(9/66, 95%CI 6,4-23,3%) of CF patients diagnosed in infancy had this presentation.[145] The equivalent figure in Cape Town was lower (9,5%, 10/105, 95%CI 4,7-16,8%). However if only those born in the second half of the study period (when awareness had risen) are included, the incidence was 16,4% (9/55, 95%CI 7,8-28,8%). Prospectively this presentation was found in 2 out of 49 (4%, 95%CI 1-14%) patients screened for CF in Wisconsin trial.[139] In this trial few patients had had sweat test before 6 weeks of age. Most reports show that the signs and symptoms of this complex are present as early as this, suggesting that this incidence for this presentation (albeit with wide CIs) represents as accurate a figure as is possible at the moment in developed countries. It cannot therefore be shown conclusively that the presentation is more common in Cape Town but the suspicion that it is remains. This suspicion is intensified by the ethnic distribution of our cases. This is unlikely to relate to CFTR genotype as, by definition, this presentation is a severe one and more white CF patients have ΔF508 homozygosity (a severe CFTR genotype) than coloured patients do. Delay in diagnosis cannot be blamed either. It must therefore be considered that socio-economic differences between the groups are playing a role in this phenomenon, presumably through nutritional mechanisms.

Further complicating the diagnosis of CF in this presentation is the unreliability of the sweat test in the presence of oedema. Some studies have shown that sweat chloride levels are often low in the oedematous phase, rising to typical CF levels as the oedema clears.[143] CF cannot be excluded as the cause of the syndrome until the oedema is gone. The main problem experienced with the sweat test in this situation in our hands has been difficulty collecting enough sweat from oedematous infants. From the early 1990s, when faced with this situation, we have sought a molecular diagnosis while starting PERT and vigorous nutritional rehabilitation. With the advent of the human faecal pancreatic elastase 1 test, testing for PI and/or starting PERT early can lead to a diagnosis and rapid amelioration of this potentially lethal nutritional state. The mortality associated with the anaemia/oedema complex is discussed in Chapter 9.

Initially recognised as a complication in known CF cases in heat wave conditions such as those in New York in 1948,[146] electrolyte derangements as a presentation of CF have

been recognised since the 1950s. Their relative frequency was initially put at 46% (5 out of 11 patients diagnosed in infancy) in Tucson, Arizona.[147] This high frequency has not been reproduced elsewhere and may relate to the hot, dry Arizona climate. In Cape Town, which is very hot in mid-summer, only 3,4% of presentations were due to this complication. Among those who presented in infancy, its frequency was 5,7% (6/105). More recently a study from Eastern Europe showed 16,5% of infants to have had this complication.[148] It is conceivable that cases are missed in Cape Town. The annual summer diarrhoea epidemic takes its toll and among these deaths there may be children who have CF and die from the severe metabolic derangement associated with the excess salt loss before the tell-tale metabolic alkalosis, never a biochemical feature of dehydrating diarrhoeal disease, can be identified.

Rectal prolapse was never the only pointer to CF in this series. This is consistent with the findings of Zempsky and Rosenstein who reviewed 54 children presenting with rectal prolapse.[149] Six of them proved to have CF and all 6 had other features of CF present when the rectal prolapse developed.

Fitzsimmons, in the largest study to appear up till then, presented the data from 17,857 patients in the US National CF Patient Registry as it stood in 1990.[140] Seventy percent of patient had been identified in infancy, 80% by 4 years of age and 90% by age 12 with a median of 7 months. Our figures compare well with these with medians and means being slightly lower. The absence of adult-age diagnoses in our cohort means that our figures cannot be taken as better than the USA ones, but nonetheless they are encouraging. However, a lower proportion of CF patients were diagnosed in infancy in the Western Cape province compared to the USA, indicating that late diagnosis is still a problem here. This is further emphasised when patients without MI are compared with those from the control group (which also excluded patients with MI) from the Wisconsin CF Neonatal Screening Study (12 months in Cape Town, 28 weeks in Wisconsin).[150]

In Latin America where adverse social circumstances are not unlike those in SA, mean age at diagnosis of CF varied from 3,3 (SD 4,2) years in Argentina to 4,3 (SD 5,5) years

in Mexico in an epidemiological study published in 1991.[151] These are well above the figures for Cape Town and, while they do include persons diagnosed in adulthood, the standard deviations show that they are in the main young populations such as ours. In our region, coloured patients are generally poorer that white patients but this did not lead to later median age at diagnosis. It is likely therefore that another reason explains the significantly later age at diagnosis in Latin America e.g. greater lack of awareness of CF in the lay and medical communities. Indeed Macri and colleagues suggest that this is the case.[151]

Antenatal diagnosis was only made on one of these children and this was through the use of ultrasonography. This picked up the features of MI through the pregnancy. As Corteville and colleagues have shown, bowel wall hyperechogenicity and bowel dilatation continuing into the 3rd trimester are highly suggestive of CF.[127] This young girl proved to have MI postnatally and did well after surgery. Antenatal genetic diagnosis has not been made on any child in Cape Town. Antenatal genetic testing by amniocentesis or chorionic villus sampling has only been taken up by families planning further children after the birth of child with CF in the context of abortion of the affected fetus.

Girls were diagnosed earlier than boys in this study. This is counter to the largest study to address this issue, the North American CFF Registry study published in 2002,[137] and probably relates to the preponderance of males among those with a later diagnosis of CF (Table 4.5). If these patients are excluded, the difference ceases to be statistically significant. Using a very large cohort (11 275 subjects) the Registry study showed that girls were diagnosed a mean of 4 months later than boys, the difference being greater (18 months) if there was a respiratory presentation.[137] The reasons for this and its significance with respect to poorer life expectancies for girls remain conjectural. In this Cape Town study it is likely to have been a matter of chance that more boys than girls had later diagnoses. As shown above, many late diagnoses were due to atypical disease (e.g. PS) or identification of mildly affects older siblings – reasons that are not gender-specific.

This study covered 20 years during which changes have taken place in diagnostic techniques and the understanding of the range of ways in which CF can present. Median ages in this analysis were higher than the overall figures for the study owing to the omission of children born in the last nine years. No clear improvement in the age at which children were diagnosed with CF could be demonstrated. Given the low median ages at diagnosis, this is not surprising, although omitting the children with MI and older siblings with CF produced a larger rise in median age at diagnosis for the 1st Period (8 to 18 months) than for the 2nd Period (10 to 11,5 months). Farrell reported that in the USA from 1970 age at diagnosis fell sharply but has not fallen during the 1980s and 1990s.[152] He quotes median age at diagnosis in the USA to have been 0,5 years among the 900 patients diagnosed in 1996, but the inclusion of screened patients make this figure difficult to compare with the median age of 10 months in the 2nd Period in this Cape Town study. Hill and colleagues in the 1980s studied CF in an earlier generation of South Africans many of whom had been born in the 1960s and 1970s.[33] Mean age at diagnosis was 20,6 months, much like that presented here. Unfortunately median age at diagnosis was not given, however would have been less than 1 year overall as 63% of patients had been diagnosed by that age. In the present study 88,4% of patients were diagnosed by the age of five years compared with 74% in Hill and colleagues' study. All in all these trends suggest that a modest reduction in age at diagnosis has occurred in the last three decades in this region.

Recent evidence from the CFF Registry has suggested that mode of and age at presentation of CF can influence survival.[153] These aspects will be discussed further in the chapter on the prognosis of CF (Chapter 9).

CONCLUSION

In the Western Cape province CF presents much as it does in other parts of the world. Overt malnutrition and the typical diagnostic triad are often not present requiring clinicians to think of CF in other clinical situations e.g. patients with persistent, recurrent or severe respiratory symptoms without overt nutritional depletion. The anaemia/oedema complex is particularly common in this region among coloured patients, perhaps

mediated through socio-economic factors. Age at diagnosis compares favourably with better resourced countries and may have improved over the period covered by the study. There is room for further reductions in age to diagnosis. There are demonstrable benefits to early diagnosis but, since population screening is not yet justifiable in this context for reasons of prevalence, cost and logistics,[43] this will only be brought about if greater awareness of CF is created amongst the public and in the health services of this region.

PART TWO: CLINICAL FEATURES OF CYSTIC FIBROSIS

For the purposes of the chapters that cover clinical aspects of CF, the manifestations and patterns of CF disease seen in the Cape Town population will be divided into the three groups described in the introduction to this chapter:

1) Those clinical features directly due to CF. These features are the result of dysfunction of organs and consequent damage to the same organ. PI would be an example in this group.
2) Clinical features resulting from secondary effects of CF-related organ dysfunction and damage. These may be features affecting the whole person (e.g. malnutrition) or other organ systems (e.g. the bones).
3) Clinical features resulting from therapy for clinical CF disease.

Classification of certain complications of CF into one of these groups is not always a simple matter given the complexity or the uncertainty of their pathogenesis. The following section that explores current understanding of the development and characteristics of the clinical features of CF will discuss these difficulties.

GROUP 1: Clinical features directly due to CF

THE LUNGS

In view of frequency, complexity and threat to survival, the lung disease of CF is its most important feature. Almost all persons with CF have significant lung disease. The lung disease is responsible for most illness and therapy and it kills almost all CF patients. While the exact pathogenesis remains unknown, CF lung disease is characterised by

endobronchial inflammation and infection that leads to chronic obstructive and suppurative lung disease.[154] Respiratory failure is the end result of this progressive process.

Because of its importance, the lung disease of CF merits a chapter on its own. The studies in the present chapter aim to present the pattern of manifestations of CF in Cape Town. Thus, with respect to the lung disease, its presence or absence in the patients will be noted and specific major complications of CF lung disease in this population will be dealt with in this chapter. Details of infections and pulmonary function are the focus of Chapter 7. The progressive lung disease of CF can lead directly to four major complications:[154]

Empyema

Rare in the antibiotic era, the development of empyemata with lower respiratory tract infections in CF patients was not uncommon before then. Shwachman and colleagues described two cases in 130 patients whose CF had been diagnosed before the age of 3 years.[128] Taussig and colleagues described four cases all of whom had empyema in infancy before the diagnosis of CF was made.[155] The most common causative organism was *S aureus*. Since that time and with the introduction of powerful anti-staphylococcal antibiotics, this complication has been reported even less frequently.

Massive Haemoptysis

This serious complication of CF lung disease has been defined as the coughing up of >240ml of blood per 24 hours or the recurrent bleeding of substantial volumes of blood (>100ml) regularly.[154] This complication is very uncommon in the childhood years. After the age of 16 years it occurs in about 1% of patients each year. The bleeding comes from bronchial arteries that have become greatly enlarged and tortuous. Management consists of the reduction of risk factors for bleeding (Vitamin K deficiency, the use of non-steroidal anti-inflammatory drugs) and pro-coagulant drugs such as tranexamic acid. If these measures fail to stem the flow, the bleeding bronchial artery will need to be occluded through embolisation using interventional radiological techniques.[154]

Pneumothorax

This complication occurs in the presence of significantly damaged lungs. It is thought to occur when a cystic cavity or bleb on the surface of the lung bursts into the pleural cavity. It tends to occur in older patients and, while treatable, is a sign of a poor prognosis.[156] Pneumothoraces may recur and, when this happens, often require pleurodesis.[154]

Cor pulmonale

Pulmonary hypertension in CF is a consequence of the chronic lung disease. It is difficult to diagnose in the absence of clinical signs of right heart failure such as an elevated jugular venous pressure and peripheral oedema. Electrocardiography and echocardiography are not sensitive tests of the cardiac effects of pulmonary hypertension in the context of CF. Cor pulmonale is a very late manifestation in CF.

THE PANCREAS

Pancreatic insufficiency

PI occurs as a result of blockage of pancreatic ducts by inspissated secretions as a result of low water and electrolyte efflux from ductal cells. These digestive enzyme-rich secretions cause autodigestion of the pancreas. Pathologically there is fibrosis and cystic change with loss of glandular acinar tissue. (These macroscopic features led to the soubriquet Fibrocystic Disease of the Pancreas, an early name for CF.[7]) In the majority of cases this process is well advanced by the time of birth.[157] The resultant PI leads to nutrient malabsorption from the initiation of feeding. In a minority of patients, PI develops later in life. In a screened population, about a third of babies do not have PI at birth.[157] Between 10 and 15 % of CF patients never develop PI.[158 159]

The main clinical manifestation of PI is steatorrhoea which impacts on the child's growth unless there is a proportionate increase in calorie intake through increased appetite.[160] Malabsorption of fat soluble vitamins also occurs as a result of PI.

Fat malabsorption can be suspected on stool inspection when free fat may be seen and proven using a 3-day stool fat measurement. The origin of this malabsorption can be shown to be pancreatic by the absence of proteases of pancreatic origin in the stool (chymotrypsin or faecal-1-human pancreatic elastase). These tests, while desirable, are not essential to the diagnosis in the presence of obvious steatorrhoea and growth failure.

Diabetes mellitus

The pancreatic destruction and fibrosis caused by abnormal ductal function as a result of the CFTR abnormality in the ducts leads to damage of pancreatic tissues that do not express CFTR. The Islets of Langerhans have insulin producing cells. These cells (β cells) are reduced in number in CF. The exact pathogenesis of CF-related diabetes mellitus (CFRD) is not fully understood as β cell numbers do not differ between those with and those without the complication.[161] The complication is at the severe end of a continuum of abnormalities of glucose tolerance in CF, being defined as fasting hyperglycaemia with a 2-hour peak glucose level >11,1mmol/l on the oral glucose tolerance test (OGTT) or through typical symptoms of diabetes mellitus: polydipsia and polyuria in association with hyperglycaemia.[162]

CFRD is unusual before the second decade of life. The proportion of CF patients with diabetes mellitus rises with age. CFRD is an indication of a relatively poor prognosis.[163]

CFRD differs from both Type 1 and Type 2 diabetes mellitus. Unlike the former, ketoacidosis is unusual and auto-antibodies are not present. Secretion of the gluconeogenic hormone glucagon is also decreased in CFRD. Insulin resistance, the cardinal feature of Type 2 diabetes mellitus, may be found in CFRD (most commonly in association with acute pulmonary exacerbations) but not to the same degree and not in association with obesity, the other cardinal feature of Type 2 diabetes mellitus.[161]

There is growing evidence that the glucose intolerance that precedes full blown CFRD is detrimental to the health of CF patients.[164] Lung function deteriorates in this phase despite the absence of symptoms of diabetes mellitus. There is a strong move towards

screening for CF-related glucose intolerance using glucose tolerance tests in older children and adolescents with CF. Currently this is not the policy at the RCCH.

Pancreatitis

Acute or relapsing pancreatitis is an unusual complication of CF. It usually occurs beyond the early childhood years and used to be thought to be exclusive to who have PS.[134] This has been shown not to be so with significant numbers of CF patients with PI developing pancreatitis.[165] It typically presents with recurrent abdominal pain and should be considered when a CF patient has this symptom.

THE GASTROINTESTINAL TRACT

Meconium ileus

Since MI causes severe clinical disease early in the neonatal period, it is a presenting feature of CF as has been discussed above (p109). It occurs in about 18% of CF patients.[153] It may be complicated by meconium peritonitis or intestinal atresia. Because MI usually requires the services of surgeons, it will be discussed in detail in the next chapter (Surgical Aspects of CF). The meconium plug syndrome in which there is delayed passage of meconium after birth until a meconium plug is passed is an occasional variation on the early intestinal obstruction group of CF presentations.

Distal intestinal obstruction syndrome

A cause of intestinal obstruction after the neonatal period, the distal intestinal obstruction syndrome (DIOS) used to be called the meconium ileus equivalent following a 1962 paper by Jensen.[166] It is not an equivalent to MI, so that name has dropped from usage. The term DIOS was introduced by Park and Grand in 1981.[167] DIOS results from maldigestion and CF-induced changes in intestinal motility. It might be considered to be secondary to PI as it is unusual in patients with PS,[168] but the consequences of CFTR dysfunction in the gastrointestinal tract also contribute to the syndrome, hence its inclusion in this section.

In DIOS there is an accumulation of the products of maldigestion mainly in the ileum and the right side of the large colon. It is likely that decreased intestinal motility and other gastrointestinal factors such as abnormal mucus contribute to this accumulation. The clinical effect is to produce colicky abdominal pain associated in many but not all cases with symptoms (vomiting, constipation) and signs (abdominal distension) of intestinal obstruction. Anorexia may also be a consequence. Often a right lower quadrant abdominal mass is felt. Faecal masses may also be felt elsewhere in the abdomen.

DIOS can occur at any age, is often recurrent and may be associated with inadequate PERT. It may present acutely or less severely over many weeks and months. This latter presentation of DIOS can contribute to anorexia and poor growth. There is an overlap in the clinical features and pathogenesis of DIOS and 'functional' faecal loading in CF. Both have recurrent abdominal pain and a build up of faecal material in the colon. The mode of treatment (purging and attention to optimising PERT and diet) is also similar.

An exact definition of DIOS is hard to come by. The triad of intestinal obstruction, severe abdominal pain and a right lower quadrant abdominal mass equated to meconium ileus equivalent and is what Park and Grand meant by DIOS, though they say that a chronic form may occur.[167] In their review, Rosenstein and colleagues do not define DIOS.[169] They list a series of symptoms and signs and report a 41,3% incidence of DIOS among 68 patients. Rubinstein and colleagues studying a larger cohort (168 patients) coupled constipation and DIOS.[170] The former required there to be a reduction in stool frequency. This is not a necessary feature for the diagnosis of functional faecal loading meaning that cases of functional faecal loading were not included in this group. 'Meconium ileus equivalent' required 'severe' abdominal pain in this study meaning that only the acute form was studied. This approach leaves out many cases with recurrent abdominal pain and faecal loading who may have had DIOS. Thus this study's incidence for DIOS of 9% is an underestimation.[170]

In practical terms, abdominal pain (acute or recurrent) and clinical and/or radiological evidence of retention of faecal matter in the right colon and beyond tend to lead to the

diagnosis of DIOS in a CF patient. For the purposes of this review, abdominal pain with faecal retention with or without other symptoms of intestinal obstruction is considered to be evidence of DIOS unless another cause was found.

Rectal prolapse

Rectal prolapse, as was discussed with the presenting features of CF (p126), is associated with untreated or poorly controlled steatorrhoea. Kulczycki and Shwachman noted that, untreated, 22,6% of patient had prolapse but only 2 out of 106 on treatment had it.[171] Once the diagnosis of CF has been made and PERT established, its appearance strongly suggests poor adherence to therapy. Thus rectal prolapse tends to be a presenting feature of CF and is unusual after that.

Intussusception

This complication of CF occurs in about 1% of cases.[172] Unlike in non-CF patients in whom intussusception occurs in early infancy, it occurs later in childhood and can even happen in adulthood. It is thought that the sticky, maldigested intestinal contents of CF form a lead point for the intussusception. Bloody stools, a cardinal feature of intussusception in infants, are unusual in the form that occurs in CF patients.

Crohn's disease

Inflammatory bowel disease can occur in the context of CF and, according to an active case finding study by Lloyd-Still,[173] is more common in CF that in the general population. It is likely to be an immune response to the abnormal contents of the CF bowel. The diagnostic criteria are the same as in non-CF patients.

THE HEPATOBILIARY SYSTEM

Focal biliary cirrhosis

As with other water-based secretions in CF, bile is abnormal. As a result of CFTR dysfunction in cholangiocytes,[174] hydration of bile is inadequate.[175] The exact pathophysiology beyond this point is not yet clear. There is sludging of bile in the canaliculi of the liver causing obstruction. Consequent on this are focal areas of necrosis.

Gradually over many years this may lead to multilobular biliary cirrhosis. Toxicity of taurine-poor bile is another putative factor leading to liver damage. Abnormal function of stellate cells, perhaps secondary to the abnormal bile, has also been implicated in the prominent fibrosis that occurs.[175]

This process is usually clinically silent. To palpate a liver in CF is often normal, particularly where there is significant lung overinflation. An enlarged liver may be due to steatosis, an association with severe malnutrition. The palpation of a *firm* hepatomegaly should lead to consideration of developing biliary cirrhosis. Signs of portal hypertension such as splenomegaly develop in a proportion of cases, leading in some to complications such as bleeding oesophageal varices. Hepatic encephalopathy is unusual in CF owing to the relative sparing of hepatocyte function.

With the advent of a therapy that can potentially delay progression to biliary cirrhosis, ursodeoxycholic acid (UDCA), an effort is being made to diagnose CF-related liver disease earlier in its course using regular abdominal ultrasound and serum liver enzyme estimations. Whether this will have a effect of the incidence of serious complication is not yet proven.[176]

The onset of CF-related liver disease seems to be almost exclusively in childhood and adolescence.[177] How common CF-related liver disease is is a matter of some debate owing to the use of varying diagnostic criteria in the studies (anything from 1,4 – 43%). It appears invariably to be associated with PI.[177]

Cholestasis in infancy

The biliary obstruction associated with CF can produce a neonatal hepatitis-like syndrome in early infancy.[131] Clinically this can be indistinguishable from other causes of the syndrome such as congenital infection. Sweat testing should be a routine part of the work-up for this presentation. A child with CF who presents like this will not necessarily continue to have significant liver disease. It is reported to occur in about 2% of cases. PI is an invariable correlate.

Gallstones

Cholelithiasis in CF usually occurs in adulthood and is not common.[178]

THE UPPER RESPIRATORY TRACT

Rhinosinusitis

As with the lower respiratory tract, the upper respiratory tract is dysfunctional when CFTR is abnormal. Airway clearance is compromised leading to more infections which take longer to clear and become chronic. Nearly all children with CF develop hypertrophy of the nasal sinus mucosa leading to complete filling of the cavity seen radiologically as opacification.[179] However, significant symptoms occur in fewer children. Acute sinusitis with its typical symptoms of fever, congestion and facial pain is unusual in CF. Rather there may be chronic ill health, anosmia, intermittent fever, persistent nasal obstruction with or without continuous purulent nasal discharge and headaches.[179] The bacterial causes of this are the usual upper respiratory tract pathogens such as *Streptococcus pneumoniae* as well as typical CF-associated bacteria such as *P aeruginosa*. The contribution of the paranasal sinus disease to the poor health of children with CF is often underestimated making prevalence figures difficult to establish. Compounding this difficulty is the overlap with allergic upper respiratory tract symptoms and signs.

Nasal polyposis

The nasal polyps of CF are a direct result of the mucosal hypertrophy just discussed. They are common in CF, occurring in 10-32% of cases in most series.[179] Asymptomatic polyps may be seen if rhinoscopy is a routine procedure at follow up visits. Symptoms are usually those of nasal obstruction. Some patients are troubled by repeated bouts of obstruction despite surgical removal of the polyps. Surgical management of polyps is discussed in Chapter 5.

Nasal polyposis may be the presenting feature of CF. Testing for CF is recommended when a child has nasal polyps.

THE GENITAL TRACT

Male and female infertility are mentioned here for completeness' sake. They are unlikely to be complained of in childhood or adolescence. Almost all males with CF have no vas deferens and this may be noted clinically in childhood when no spermatic cord is palpable.

GROUP 2: Clinical features secondary to CF-related organ dysfunction

Nutrient deficiency

This is by far the most important secondary feature of CF. Chapter 6 is devoted to a discussion of growth and nutrition and its correlates in CF and covers five studies undertaken in Cape Town. It will not be discussed further in this chapter.

Anaemia/oedema complex

This manifestation of CF was first described in the 1940s. It is usually seen in the context of exclusive breast feeding or soya formula feeding. Its cardinal feature is oedema resulting from hypoproteinaemia which relates to the lower protein content of breast and soya milk. Variably associated with the oedema is a haemolytic anaemia secondary to vitamin E deficiency, itself due to fat malabsorption, and a rash caused by vitamin and mineral deficiency. Alban and colleagues have suggested that children with this feature of CF do worse than others, possibly because of a delay in diagnosis.[180] Five of the 9 infant deaths reported from the RCCH in 1994[138] were associated with this complex.

Gastro-oesophageal reflux

Incompetence of the gastro-oesophageal junction has been described commonly in association with CF. It occurs with increased frequency in both young and old with CF, leading to worsening of lung disease, and gastrointestinal symptoms from oesophageal dysmotility and oesophagitis. It is thought to be caused by changes in acidity in the proximal small bowel and to changes in diaphragmatic tone and shape secondary to lung

overinflation.[181] It can be demonstrated with contrast radiography, ultrasound, scintigraphy or pH studies.

Peptic ulcer disease

The pathogenesis of peptic ulcer disease in CF may relate to stress (as suggested by Littlewood[181]) or the altered gut microenvironment associated with poor alkalinisation of the duodenum.

Osteoporosis

The pathogenesis of bone disease in CF is complex involving calcium and protein metabolism, nutrient malabsorption, vitamin D, high levels of inflammatory cytokines, reduced activity levels and pubertal delay.[182] What is clear is that, at least during childhood, it can be prevented. Salamoni and colleagues in Switzerland saw no evidence of bone mineral density disorder in normally nourished CF patients.[183] Silent in the childhood years, osteoporosis is becoming a significant source of symptoms as CF populations age. This is particularly evident in the vertebral column where microfractures and collapse of vertebral bodies lead to back pain. Fractures of limb bones are also seen.

Saitowitz studied the calcium and vitamin D status of children in Cape Town in the late 1990s.[184] Half took in insufficient calcium but almost all had normal levels of 25-hydroxy vitamin D, calcium, phosphate and alkaline phosphatase. Bone mineral density was not studied. All children have received supplemental calcium since then.

Arthritis

This takes two forms. One is hypertrophic pulmonary osteoarthropathy, the same entity that can occur with any chronic suppurative lung disease. The other form is rheumatoid in nature, affecting mainly large joints. It is sero-negative and is not usually destructive.[185] It occurs in the context of high circulating levels of immunoglobulins as a result of the chronic inflammation in the lungs.

Reactive depression

Depression is included in this group because, although it is not an organ-based entity, it is a serious concomitant of CF. It has direct effects on the physical health of those with CF. Its cause is multifactorial, involving reactions to physical disease, perceived and actual problems and family/social circumstances. Clinicians need to be alert to its appearance, often subtle, in their CF patients.

Allergic bronchopulmonary aspergillosis (ABPA)

Aspergillus fumigatus can colonise the airways of CF patients. In some it is a commensal, but in others it induces an immune response. This response has elements of Types I and III hypersensitivity reactions producing IgE and IgG antibodies. These in turn react with the organism's antigens at the airway surface inducing inflammation. The dominant clinical effect of this is airway obstruction manifesting as wheezing. Radiologically, lung infiltration may be seen. ABPA should be thought of if a deterioration of lung function occurs in a CF patient and there is a poor response to antibiotics or if the wheezing is persistent or dominates.[186]

Because *A fumigatus* and the antibodies may be present without clinical disease and because ABPA in CF differs from that associated with asthma, diagnostic criteria as set out in Box 4.1 have been recommended.[187]

Box 4.1. Diagnostic criteria for acute bronchopulmonary aspergillus in cystic fibrosis patients (Reference 187)

All immunologic parameters required
- SPT positive to Af and IgE-Af (RAST)
- IgE elevation >500 iu/ml[2]
- IgG antibodies to Af or precipitins
- Hypereosinophilia[1] >400/ml
- Reduction by >50% in IgE after 2 weeks of daily systemic corticosteroid therapy

Supportive (at least 3 required)
- Airway obstruction/wheezing
- Bronchiectasis on chest CT
- Pulmonary infiltrates on chest radiograph
- Af in sputum culture
- Decrease in pulmonary function (>19% decrease in FEV_1)

[1] Hypereosinophilia not required when on systemic steroids
[2] 1 iu = 2.4ng
Af – *Aspergillus fumigatus*
CT – computed tomography
FEV_1 – forced expiratory volume in 1 second
SPT – skin prick test
RAST – radioallergosorbent test

Treatment is with glucocorticoids. The role of anti-fungal drugs such as intraconazole is not yet established.[188]

Hyponatraemic dehydration/metabolic alkalosis

As discussed in the section on the presentation of CF (p76), excessive electrolyte loss in the sweat can lead to electrolyte depletion.[148] When this happens over time, it may manifest with anorexia, weakness and poor growth. Metabolic alkalosis with hypochloraemia, hypokalaemia and hyponatraemia is typical (pseudo-Bartter's syndrome). More acutely (for example, after exercising in hot conditions), CF patients may present with heat prostration. Hyponatraemia is found on electrolyte testing. It was this manifestation of CF during a heat wave in New York in 1948 that led to the development of the sweat test in the 1950s.[146]

Other conditions

The literature names a few other conditions that have been associated with CF: volvulus of the bowel beyond infancy,[189] coeliac disease[181].

GROUP 3: Clinical features secondary to CF treatment

Given the large number of therapeutic interventions associated with the treatment of CF, patients are put at risk of side effects and complications. Some misadventures may be associated with the drugs, others with hospitalisation, others with procedures. Some risks are known e.g. fibrosing colonopathy associated with high doses of certain forms of PERT;[17] increased risk of antibiotic allergy with time and exposure.[190] Others are idiosyncratic. It may not always be easy to attribute a symptom to an intervention leading to underdiagnosis of its side effects. Conversely patients and their parents may attribute symptoms to certain therapies erroneously. Formal monitoring for some known side effects may be undertaken e.g. audiometry to check for aminoglycoside toxicity. Making measurement of side effects and complications of therapy difficult can be the length of time between the initiation of the intervention and the development of harmful consequences. It is important that therapeutic teams are aware of the potential for their interventions to do harm. Audit of new and tried therapies can go some way to measuring any harm that may be occurring.

Study 4.2 was undertaken to attempt to quantify the spectrum of clinical features of CF seen in the CF population cared for at the RCCH.

Study 4.2 Clinical features and complications of cystic fibrosis in the Western Cape province

Objectives

1) To determine the range and rates of clinical features and complications of CF seen in the Western Cape province.
2) To determine the age at which individual clinical features of CF appear in the Western Cape province

3) To determine whether 'ethnic group' influences the frequency or appearance of the clinical features and complications of CF in the Western Cape province
4) To determine whether CFTR genotype influences the frequency or appearance of the clinical features and complications of CF in the Western Cape province

Methods

Study population

The 181 CF patients described in Chapter 2.

Data collection

The following data were extracted from the patients' hospital folders in a chart review:

1) Demographic features
2) CFTR genotype: Homozygous for ΔF508, heterozygous for ΔF508, no ΔF508, not tested.
3) Clinical features: The presence of the clinical features and complications of CF and the child's age at their recognition were recorded. Following the structure used in the Introduction to this study, Table 4.6 lists and defines the features sought in the clinical record and classifies them according to organ system. Group 1 contains features and complications directly caused by CFTR dysfunction. Group 2 contains features and complications that occur secondary to primary CF-related organ dysfunction. In addition, complications of therapy (Group 3) were recorded where identified as such by a clinician. [Complications associated with surgery and anaesthesia are recorded in Chapter 5.]

Table 4.6 Clinical features and complications of cystic fibrosis

Organ system	Feature or Complication	Definition
GROUP 1		
GIT	Pancreatic insufficiency	Ongoing abnormal stools or steatorrhoea when not on pancreatic enzyme replacement therapy (PERT) or On PERT. (Proven high faecal fat estimation not needed)
GIT	Meconium ileus (MI)	Clinician report in notes
GIT	Complicated MI	MI with peritonitis or intestinal atresia
GIT	Rectal prolapse	Clinician report in notes
GIT	Distal intestinal obstruction syndrome	Recurrent abdominal pain associated with radiological evidence of intestinal obstruction and/or faecal loading in the right colon or Intestinal obstruction with no other cause identified.
GIT	Intussusception	Clinician report in notes
GIT	Ileitis/Crohn's disease	Clinical, radiological and histological features consistent with the diagnosis.
GIT	Liver disease	Persistently abnormal liver (size, shape or consistency) on palpation and/or Two or more raised transaminase levels separated by an interval of more than 3 months and/or Abnormal ultrasound liver features
GIT	Complication of portal hypertension	Clinician report in notes
GIT	Infantile cholestasis	Cholestatic jaundice in an infant, no other cause found
GIT	Liver failure	Clinician report in notes
Respiratory	Massive haemoptysis	Coughing up of >240ml of blood per 24 hours or the recurrent bleeding of substantial volumes of blood (>100ml) regularly
Respiratory	Pneumothorax	Clinician report in notes
Respiratory	Empyema	Clinician report in notes
Respiratory	Cor pulmonale	Clinical features of heart failure in the presence of severe lung disease
Respiratory	Nasal polyposis	Nasal polyps seen on inspection on more than one occasion
Respiratory	Rhinosinusitis	Persistent nasal obstruction not responsive to anti-allergic therapies and/or Clinician report in notes
Other	Diabetes mellitus	Symptomatic glycosuria and hyperglycaemia

Table 4.6 continued

GROUP 2		
GIT	Anaemia/oedema complex	Oedema due to hypoproteinaemia with or without anaemia, failure to thrive and a nutritional skin rash
GIT	Gastro-oesophageal reflux disease (GORD)	Symptoms consistent with GORD and positive investigation for gastro-oesophageal reflux.
Other	Bone and joint disease	Arthritis in a child with significant chest disease Back pain or fractures in a child with osteoporosis
Other	Reactive depression	Clinician report in notes
Respiratory	Allergic bronchopulmonary aspergillosis	Immunological evidence of infection with *Aspergillus* species associated with persistent respiratory symptoms not responsive to antibiotic therapy
GIT	Peptic ulcer disease	Endoscopic report in notes
Other	Hyponatraemic dehydration/ metabolic alkalosis	Blood results consistent with this complication

Results

Table 4.7 shows the incidence of the features of CF from Group 1 in this population. Ninety five percent (95% CI 90,8-97,7%) had PI. MI affected 15% (95%CI 9,7-20,1%) of cases (white 16,8% [17/101], coloured 13,3% [10/75]). The patient with intussusception had three episodes of bowel obstruction.

Table 4.7 Direct clinical features of cystic fibrosis in 181 patients

Group	Clinical feature or Complication	Number (%)	Median age at onset (months)	Range
GIT	Pancreatic insufficiency	172 (95)	Not recorded	
	DIOS	41 (22,7)	98	5 - 169
	Meconium ileus	22 (12,2)	Birth	
	Complicated meconium ileus	5 (2,8)	Birth	
	Rectal prolapse	15 (8,3)	18	5 to 43
	Crohn's disease	1 (0,6)		
	Intussusception	1 (0,6)		
	Liver disease	17 (19,4)	108*	7 – 152*
	Complications of portal hypertension	5 (2,8)	110*	74 – 189*
	Infantile cholestasis	1 (0,6)		
Respiratory	Lung disease	180 (99,4)	Not recorded	
	Pneumothorax	3 (1,8)	164	116 - 207
	Massive haemoptysis	1 (0,6)	194	
	Cor pulmonale	11 (6,1)	118	75 - 248
	Empyema	1 (0,6)	67	
	Nasal polyposis	19 (10,5)	97	4 - 200
	Rhinosinusitis	6 (3,3)	60	19 - 95
Other	Diabetes mellitus	8 (4,4)	192	109 - 242

GIT – Gastrointestinal tract
DIOS – Distal intestinal obstruction syndrome
* Age at onset unclear in 2 patients (one <5 years [liver disease only], one <9 years [liver disease and portal hypertension])

Only 9 patients (6 coloured, 3 white) remained pancreatic sufficient. None of those with PS was ΔF508 homozygous; 3 had a single copy of the mutation. Median age at diagnosis had been 71 months (range 0 – 169 months) compared to 6 months for the whole population. All except three had mainly lower respiratory tract symptoms when diagnosed. One of the three only had nasal polyposis and was diagnosed at 11 years of age, one had MI, and the other was the asymptomatic sibling of a girl with CF who had PI.

The 17 patients with CF-related liver disease and their modes of diagnosis are shown in Table 4.8. There was no difference in incidence between gender, ethnic or genotype groups. All patients with CF-related liver disease also had PI. Five of the 17 patients had had MI. Two other patients had severe liver disease whose connection with CF was not

clear. One of these, a boy, presented with hepatomegaly at four years of age. Liver biopsy showed typical features of chronic active hepatitis. He did not have immunological features of the disease. Chest disease became significant late in this life and CF was diagnosed when he was 14 years old. Review of liver histology confirmed the chronic active hepatitis; no features suggestive of CF were seen. He did not have fat malabsorption on 3-day stool fat estimation. He developed portal hypertension with bleeding oesophageal varices and died in liver failure at the age of 17 years. The second child, diagnosed with CF owing to meconium peritonitis and malnutrition, had not had evidence of liver disease until the sudden development of a Reye-like syndrome with hepatomegaly in his second year of life. He died during this episode. A *post mortem* showed cerebral oedema.

The complications of portal hypertension in Table 4.8 were bleeding oesophageal varices (3), bleeding diathesis (1) and severe abdominal pain from splenic infarction (1).

Table 4.8 Cases with liver disease and its complications

Number*	Age (years)	Gender	Ethnic group	Mode of diagnosis	Symptomatic PHT (Age at onset in years)
170	<1	M	W	Hepatosplenomegaly	No
136	<1	M	W	Hepatosplenomegaly	Yes (7)
27	3	M	C	Firm hepatomegaly	Yes (14)
1	3	M	C	Firm hepatomegaly	No
73	4	M	W	Hepatosplenomegaly	No
34	<5	M	C	Hepatosplenomegaly	No
133	7	F	C	Hepatomegaly / raised liver enzymes	No
105	8	F	W	Raised enzymes / coarse echogenicity	No
5	<9	F	W	Hepatosplenomegaly	Yes (<9)
84	9	M	W	Firm hepatomegaly / inhomogeneous liver	Yes (13)
83	9	F	W	Hepatosplenomegaly	No
4	9	M	W	Hepatosplenomegaly	No
15	10	F	W	Firm hepatomegaly	No
49	11	M	W	Hepatosplenomegaly	Yes (15)
72	12	M	W	Firm hepatomegaly	No
95	12	M	C	Firm hepatomegaly	No
55	14	M	W	Firm hepatomegaly	No

* see Appendix A
PHT – Portal hypertension
M = Male, F = Female
C = coloured, W = white

The infant with cholestasis had had complicated MI with atresia following an intrauterine volvulus. He did well peri-operatively and had no jaundice. Icterus developed at the age of 6 months in association with severe crying. Examination showed hepatosplenomegaly and mild jaundice. Both alanine transferase and alkaline phosphatase levels were over three times the upper limit of normal. Ultrasound of the liver showed increased echogenicity of the liver with dilated extra- and intra-hepatic main bile ducts that were filled with echogenic material. Treatment with UDCA to promote choleresis was commenced. The jaundice cleared within a week. Liver function and ultrasound features had returned to normal a month later but the hepatosplenomegaly persisted.

Of the conditions in Group 2, 10 had the oedema/anaemia complex, 9 had ABPA, 8 had hyponatraemic dehydration/metabolic alkalosis, 5 had reactive depression, one had arthritis and one had recurrent back pain as a result of osteoporosis. Peptic ulcer disease manifested as a gastric ulcer in one child (who eventually required surgery to cure it – see Chapter 5 p209) and duodenitis in another two. The former presented with recurrent abdominal pain and the latter with GIT bleeding. Three other significant abdominal emergencies that probably relate to the effects of CF on the GIT were an episode of appendicitis with perforation in one child, a volvulus in a teenager and a lethal acute colitis in an infant. This latter case may have been a pseudomembranous colitis (the child died in another hospital).

Three complications were induced by therapy. One child had pseudomembranous colitis following antibiotic therapy and one suffered a perforation of the nasal septum associated with continuous oxygen therapy. One teenager developed an erythematous rash with his first dose of meropenem.

Apart from CF lung disease and PI of which all except one child had one or both, 64,6% (117/181) had at least one additional feature or complication of CF. Sixty one had one additional feature, 33 had two, 12 had 3 and 5 had 4. Four patients had 5 or more additional features or complications of CF.

Discussion

This study has demonstrated the wide range of clinical features of CF and their variability as found in a South African population. CF lung disease and PI affected nearly all the children (only one, the child with nasal polyposis, had neither) but nearly two in every three of them (64,6%) had additional features of CF during their association with the RCCH. Some features, like MI, occurred early in life while others occurred later, for example CFRD which was only seen under the age of 10 years in one patient.

The 95% (95% CI 90,8-97,7%) prevalence of PI is higher than that reported in CF populations from Western countries. Using the definition of a patient being on PERT, the National Cystic Fibrosis Registry in the USA as analysed by Fitzsimmons showed that 92,5% of CF patients had PI.[140] As she pointed out, this is an overestimation of the prevalence of PI as the Registry under-represents those with mild disease who are more likely to have PS. Other cross sectional studies of large numbers of CF patients suggest that 10-15% have PS.[191] Studies in screened populations have shown that PS at birth is more common than this. Waters and colleagues in New South Wales, Australia found that 37% (29/78) of patients had 'substantial preservation of pancreatic function' at birth.[157] A further 6 of the 29 children developed PI by 3 years of age. In Colorado, USA, the incidence of PI in 49 screened infants was 79% and 92% at 6 and 12 months respectively.[159] Couper and colleagues described 20 patients who had PS at diagnosis (mean age 3,5 years) and developed PI after an average of 5,6 years, demonstrating that PI can develop later in childhood.[160] They also showed that the longer a patient with CF remains pancreatic sufficient, the less likely it is that he or she will develop PI. Few patients develop PI in adulthood.

There is a number of potential reasons for the higher than expected incidence of PI in our non-screened population. Firstly the diagnosis of PI was made based on symptoms and growth with tests for malabsorption not being routine. As shown in Study 4.1, 24% of patients presented with respiratory symptoms alone. However almost all of these were on PERT at the time of this study. It is likely that poor weight gain and/or the recognition of

GIT symptoms by the family once the diagnosis had been made and CF discussed with them led to the assumption of PI and the introduction of PERT. A second reason is the relatively young age of the population. Some patients with PS would not yet have been diagnosed (particularly in SA where CF awareness among practitioners and the public is low – especially of the pancreatic sufficient forms) while those who have PI are likely to be diagnosed at ages covered in this study. Of those said not to have PI, only two had formal tests for fat malabsorption of pancreatic function. One had had MI and had been started on PERT. Later, when very overweight in her teenage years, she stopped her PERT with no change in her bowel habit! Given that PERT is not without potential severe side effects and is expensive, consideration should be given to testing all children with CF who have respiratory symptoms alone for pancreatic disease. The faecal human pancreatic elastase 1 test has been shown to be very useful in this regard[192] and is now available in SA.

DIOS was the second most common gastrointestinal manifestation of CF in this population. As discussed in the Introduction (p98) and defined in the Methods, a conscious decision was made to widen the clinical definition of DIOS to include all patients with symptomatic faecal loading but excluding simple constipation i.e. the passage of hard stools infrequently. This in part reflects the practical difficulty in a retrospective survey: one is dependent on what is recorded in the notes. X-rays were not reviewed, merely the report and/or the clinician's paraphrase of it were available. It also reflects a suspicion on my part that there is a large overlap in the pathophysiologies of the ill-defined entity of DIOS and faecal loading in the CF context. The DIOS of the CF literature is thought to be precipitated by the products of maldigestion, abnormal mucus, delayed intestinal transit time and unknown changes in intestinal function in the context of PI.[181] Delayed transit time and abnormal effluent from the small bowel are also implicated in 'functional' faecal loading. Build up of faeces in 'functional' faecal loading, while mainly distal, also occurs significantly in the caecum and ascending colon. The radiological scoring system for faecal loading devised by Verrier-Jones and colleagues includes this feature.[193] Littlewood attributes faecal retention of this sort in CF to poor management of PERT, supporting an origin analogous with DIOS.[181]

Since the presentation (abdominal pain, retained faeces) and management (purging, attention to diet, laxatives) are similar, all patients with symptomatic retention of faeces were considered to have DIOS in this study. The advantage of this approach is that it gives a picture of the extent to which non-surgical lower abdominal symptoms affect our CF population. It does not however distinguish between acute and less severe episodes of DIOS. However this drawback is partly overcome by an unpublished review of admissions for CF in this population in which DIOS is one of the causes for urgent admission (most cases of the acute form) or elective (the 'chronic' form).

Just under one in four of the children and adolescents suffered at least one episode of DIOS. It is difficult to compare this with reports in the literature for definitional reasons. However Rosenstein and Langbaum using a retrospective design and entry criteria based on symptoms (including 'severe' abdominal pain) found that 26/63 (41,3%) had DIOS (one had recurrent intussusception).[169] No other studies have come near this incidence. The authors felt that this is because of their method of recording gastrointestinal symptoms. The 95% CI for the 40,3% (41,3% minus the case of intussusception) are 28 – 53,5%, still well above other studies. The upper CI for our prevalence was 28,8%, just overlapping with theirs.

Using a more rigid definition than ours that required '**postneonatal partial or total bowel obstruction unresponsive to standard laxatives**', Rubinstein and colleagues found an incidence of DIOS of 9% of 168 patients with more adults than children affected.[170]

Littlewood claimed that DIOS is rare where PERT is carefully monitored (e.g. in the Leeds CF Clinic).[181] Rosenstein and Langbaum, however, noted that adjustments made to PERT when their clinic was changing from non-enteric coated to the newer forms of PERT did not influence the symptoms of their patients.[169] They suggested that the direct gastrointestinal effects of CF may dominate in the pathogenesis of severe DIOS. It

should be noted that fat restriction was still part of the dietary regime of their patients at that time.

Rubinstein and colleagues also studied 'constipation' (i.e. reduction in stool frequency) in CF.[170] An incidence of 32% was found. This, if taken with the 9% for DIOS in the same population, may equate with our findings of 22,7% given that our definition encompasses all his DIOS cases and some of the 'constipation' cases.

Fitzsimmons' North American Registry study showed an incidence of about 2,3% of 'intestinal obstruction' as a complication of CF in 1990.[140] If infants (they presumably had MI) and those older than 20 years are excluded, the figure that would be comparable with our population would be 2% per annum. Given that our data is not annualised, it cannot be directly compared but, with about 60 patients being cared for every year at the RCCH, many more than the one patient per year predicted by the USA figure suffers an episode of DIOS.

DIOS and its potential to confuse the diagnosis of other causes of abdominal pain in CF will be discussed in the chapter on Surgery in CF (Chapter 5). Of the directly CF-related causes of abdominal pain, there were three cases: one of Crohn's disease, one intussusception and one volvulus. The child with Crohn's disease is discussed in detail in Chapter 5 (p150). The volvulus occurred in a teenage survivor of MI but at laparotomy there was no evidence of an adhesive lead point. She had been managed for DIOS including N-acetyl cysteine before it became clear that a surgical cause for intestinal obstruction was present.

MI, the third most common gastrointestinal manifestation of CF, occurred with a frequency equivalent to reports in the literature. Although there were fewer cases in the second half of the period (11 cases) versus the first half (16), this is probably the product of chance. No cases of MI in black African cases have yet been seen in recent years in SA, leaving only the historical cases[118] to show that this manifestation of CF occurs in this group. In the Western Cape province a neonate with intestinal obstruction would

almost always get through the health system to a paediatric surgeon. This suggests that, if CF among black Africans is as common as the work from the University of the Witwatersrand research suggests[50] and if MI even in a black African neonate makes a surgeon think of CF, MI must account for fewer than the 10-20% of cases seen in the other SA groups. There are plans in process systematically to investigate this question nationally (A. Goldman – personal communication). The management of MI in our experience, largely surgical, is discussed in Chapter 5.

Of the 15 children who manifested rectal prolapse, only 4 developed this complication after the diagnosis of CF. In all it was associated with ongoing nutritional problems and inadequate PERT in the months following diagnosis. Consistent with the literature, it never appeared once PERT was optimised.

Intussusception and Crohn's disease, with one case each, occurred much as might have been expected in a population of this size. The girl with Crohn's disease had no relapses which would be unusual, even on treatment, for inflammatory bowel disease unassociated with CF. Her case is discussed in detail in Chapter 5 (p150). This child was also the only child to develop a large joint arthritis, another manifestation of heightened auto-immunity.

Liver disease is often silent in CF. The extent of liver disease in our population is thus underestimated by the figures given here. The presence of liver disease in this study required findings on clinical examination and/or on investigation. In practice, ultrasound examination of the liver usually followed the finding of a firm hepatomegaly. For the early years of the study the modality was not available and it was never a routine investigation during the study period. The measurement of liver enzyme levels has only recently become part of an annual review of our patients as the evidence that UDCA may be able to alter the course of CF-related liver disease has mounted. (The youngest, healthiest patients do not have routine blood tests as part of the annual review, but they are the least likely to have significant liver disease.) Abnormally high liver enzyme levels would lead to a second test being done about three months later. Prior to this

practice being instituted, CF-related liver disease was never diagnosed solely on the basis of biochemical tests. In essence thus, liver disease in CF in Cape Town has been diagnosed on clinical findings and that is what the figures reported here reflect. Only Case 120 (Appendix A) was diagnosed on the basis of investigations alone.

As outlined in the introduction to this study, defining CF-related liver disease is problematic. In a prospective study in children, Ling and colleagues showed that 92% of 124 children had an abnormality on clinical examination, biochemistry or ultrasound during 4 years of follow up.[194] Furthermore features on any of these modalities of identification of liver disease in CF might not be present at subsequent evaluations. However this study did establish that biochemical abnormalities tend to precede ultrasonographic and clinical evidence of liver disease, but this is not invariable. Thus the prevalence of liver disease is highly dependent on the methodology used to identify it.

A prospective cross-sectional study by Carla Colombo and colleagues used clinical, biochemical and echographic assessments.[195] Clinical assessment required a *firm* hepatomegaly; biochemical assessment required at least two specimens to have raised serum liver enzymes levels; ultrasound features included hyperechogenic parenchyma, heterogeneity and nodules or features of portal hypertension. These accord well with our study in that identified patients required clinical evidence of liver disease but, unlike ours, data were collected prospectively i.e. investigations were performed systematically on all patients. This difference proves crucial: 34/189 (18%) patients had liver disease. All 189 patients were, by study design, 3 years of age and over (median age 14,4 years). Using similar criteria but a retrospective methodology, our study showed a 10,9% prevalence (16/147) patients who have survived to 3 years of age.

The North American CF registry study was unable to give prevalence figures for liver disease beyond raised liver enzyme levels (2,4%) and cirrhosis (1%).[140] How systematically these abnormalities were looked for is not specified in Fitzsimmons' report. The figures quoted for 1999 from this Registry were 6,4% for elevated serum liver enzymes levels and 2,3% for cirrhosis.[176]

The largest study specifically to examine liver disease in CF comes from the Midlands of England. The records of 1 100 patients were reviewed.[196] The patients' status as regards CF-related liver disease was taken as it stood in 1988. Diagnostic criteria were looser than ours or Colombo's were in that a single abnormal serum liver enzyme levels result was taken as evidence of liver disease (12,5% prevalence). Using clinical criteria only, 4,2% of patients had liver disease. This figure is much lower even than ours, despite having a retrospective design and an emphasis on clinical criteria in common.

An alternative method of defining CF-related liver disease was used in an assessment from Israel. Here two consecutive (at least 6 months apart) one and half times elevation in serum liver enzyme levels was all that defined non-cirrhotic liver disease.[197] Histology and ultrasonographic findings defined cirrhosis. A prevalence of 28% was found. What this high figure means in terms of clinical disease is uncertain as no clinical correlates were measured. It may be that our figures will rise towards this level as we have begun to follow a trend in taking persistently elevated serum liver enzyme levels as an indication to do ultrasound investigation of the liver and consider commencing UDCA therapy.

In a review of CF-related liver disease, Tanner maintained that, in the light of these studies, clinical criteria should be the way to diagnose this complication until an investigation such as scintigraphy is shown to be more sensitive, specific and stable.[198] The recommendations from the CFF Hepatobiliary Disease Consensus Group were broader but still based mainly on clinical criteria: CF-related liver disease can be diagnosed when 'persistent hepatomegaly (increased span of liver) or splenomegaly, a firm or hard consistency of the liver on palpation, persistently abnormal liver blood test results, complications of portal hypertension, or abnormal liver histology' are present.[176] Our results are based on a methodology compatible with these recommendations.

The Consensus group recommended that CF-related liver disease be screened for.[176] Abdominal palpation at every visit and annual liver function tests form the basis of this screening. The former of these methods has always been routine in CF care in Cape Town. Now, with the introduction of regular serum liver enzyme estimations followed, in cases with persistently elevated levels, by ultrasound investigation, the prevalence figures for this population will rise and the age at diagnosis fall. The hope is that progression to cirrhosis and its complications will be halted in at least some of the CF-related liver disease so identified with UDCA therapy.[199]

It is important to note that the retrospective and observational nature of our study precludes accurate assessment of the onset of a disease process like CF-related liver disease. Despite this drawback, in finding more cases of liver disease in older children than those under 5 years of age, our study is consistent with the literature. Also consistent with the literature is the universal presence of PI with CF-related liver disease. The apparent association of liver disease with MI and DIOS in the literature is not fully accepted and requires verification in larger, prospective studies. Our numbers are too small to contribute to this debate. For the same reason, CFTR genotype and gender, other factors that have been explored to explain why some children with CF develop CF-related liver disease and others do not, could not be explored in our small population. The role of mannose binding lectin genotypes, part of the innate immune system, in predisposing to liver disease in CF has recently raised its intriguing head.[200] Such non-CFTR genetic predispositions may lead to differences in populations with different genetic backgrounds but no such difference in incidence in CF-related liver disease was found in this genetically diverse Cape Town population.

Cirrhosis with symptomatic portal hypertension affected five patients. Their ages are consistent with the literature which shows that, in the main, older CF patients suffer the consequences of portal hypertension.[199] The number with portal hypertension was higher if asymptomatic patients are taken into account. The high prevalence of enlarged spleens at presentation gives some idea of its frequency amongst our patients. Oesophageal varices were not sought in asymptomatic patients with portal hypertension; the figures

therefore represent only those who suffered gastrointestinal bleeding and had the varices seen at endoscopy. General guidelines on health care related to portal hypertension such as the possibility of oesophageal bleeding and the need to avoid non-steroidal anti-inflammatory drugs are given in every case. Those with complications all required specialised surgical interventions which are described and discussed in detail in the following chapter.

The single child with cholestatic liver disease does not fit the typical picture of the neonatal hepatitis-like presentation of CF. Rather he seems to have had an episode of biliary colic associated with thick bile in the evolution of typical CF liver disease. This being the case, no cases of cholestatic liver disease were seen in CF. This is not surprising given that fewer than 2% of CF patients have this form of liver disease.[131] One child was referred from Pretoria with this complication during my tenure at the RCCH. This infant had had MI, a common association; those referring wondered if the child warranted a liver transplant since a portoenterostomy had failed to relieve biliary obstruction. After nutritional rehabilitation, the infant did well and returned to Pretoria. Three other children developed jaundice during follow up: two had hepatitis A; one developed jaundice in the late phase of liver disease, perhaps aggravated by a reaction to fusidic acid therapy. In our experience therefore, jaundice in a child with CF is more likely to be due to Hepatitis A than to the CF!

Nasal obstruction can be a prominent feature of CF either through continuous or recurrent rhinosinusitis or through nasal polyposis. Either can reduce quality of life and are therefore significant complications of CF. The definition for rhinosinusitis used in this study is somewhat arbitrary. Allergic nasal symptoms overlap with CF ones and a lack of response to unit-allergy remedies does not exclude an allergic aetiology. CF-related symptoms may improve on anti-inflammatory therapy. Notable though was the young age of the children affected. Persistent nasal symptoms do not seem to have been a problem in older children in the absence of polyposis or allergic rhinitis. It is possible that too much was blamed on allergy in older children whereas it was thought to be less likely in the young children. Nasal polyposis was actively sought through regular

rhinoscopy (at least in recent years), the figure therefore representing symptomatic and non-symptomatic polyps.

CFRD is only the most symptomatic of a spectrum of disorders of glucose metabolism. There is good evidence that abnormal metabolism of glucose affects health in CF before overt CFRD develops.[164] Four levels of glucose intolerance in CF are recognised, based on the OGTT. With normal glucose metabolism, the 2-hour blood glucose level does not rise beyond normal; with impaired glucose intolerance (IGT) there is no FH. CFRD without FH is the stage before CFRD with FH, which would be recognised as the most severe form of CFRD and would normally be treated. That IGT and CFRD without FH are detrimental to health in CF has been shown most convincingly by Antoinette Moran and colleagues in Minnesota, USA. FEV_1 and FVC deteriorated faster over a 4-year prospective follow up period in patients with abnormal glucose tolerance than in those in whom it was normal.[164] Moreover, the rate of decline correlated with the degree of impairment of glucose metabolism. Other studies have shown that nutritional status also declines in the pre-diabetic state; this can be reversed with insulin therapy.[201]

This knowledge has led to more active case finding using OGTT in order to prevent this decline in health. In many centres OGTTs are done annually from early adolescence. Some centres are now investigating the merit of introducing insulin therapy when there is any impaired glucose i.e. before over CFRD develops. (Case reports have presented the intriguing possibility that insulin's anabolic effects can help those whose health status is declining even when the OGTT is normal.[202])

CFRD in patients in our study was diagnosed through typical symptoms of diabetes mellitus. No formal OGTT screening has taken place. Thus the figures presented represent those with overt CFRD. As CFRD is a complication in older persons with CF, it is not surprising that the numbers with CFRD in this study were small. Mortality has been high in the first two decades of life and, in recent years, most young persons over the age of 18 years have moved to GSH. The development of CFRD after transfer to GSH was not studied.

Small numbers precluded meaningful genetic analysis. Apart from an association with more severe genotype classes,[203] no CFTR mutations have been consistently associated with this complication.

Consistent with the literature, all patients with CFRD had PI. The prevalence in this population is consistent in that seen in Toronto, Canada in children between 1 and 18 years of age[204] (Toronto 2,7%, Cape Town 4,5%). In Minnesota, USA 16 out of 200 (8%) children between the ages of 5 and 19 years had CFRD.[205] The equivalent proportion in Cape Town was 6,2% (9/145).

Half of the 8 patients with CFRD developed the complication in their 17th year, the median age of onset for the group. This age cannot be compared with the Toronto or Minnesota experiences which are reported cross-sectionally with a cut off at 18 and 19 years of age respectively. No patients presented in coma and all had their hyperglycaemia easily controlled with insulin and nutritional advice specific to CFRD. Three patients were in the final phase of CF lung disease when CFRD developed. In summary, it appears that CFRD in Cape Town was no different from that seen elsewhere. The current screening approach at the RCCH is testing for glycosuria at each visit for teenagers and random blood glucose measurement in the annual review. Random blood sugar levels are the entry point for testing for CFRD in the CFF Consensus Committee Guidelines.[206] Blood sugar testing during pulmonary exacerbations when abnormal glucose tolerance may be unmasked was also recommended by the Committee. This is not practised in Cape Town. OGTT can identify children at risk of CFRD. Whether earlier diagnosis should be sought through the introduction of OGTT screening in older children in Cape Town depends on logistical considerations. The evidence is that, for the individual CF patient, the search is worth the effort and discomfort as the early introduction of insulin therapy reverses the decline in health status associated with insulin hyposecretion. In the light of our experience, a targeted approach would seem appropriate: annual OGTTs for those with PI who reach 16 years of age. Younger

patients (but over 10 years of age) with unexplained declines in nutritional or lung function measures may merit an OGTT.

As described in the introduction to this study, pneumothorax as a complication of CF is associated with advanced lung disease. That being the case one might have expected more than three cases in a population one third of whom have died in the period under review. Although its pathogenesis is not entirely clear – is it due to destruction alone (the high incidence of cysts in the lungs of CF patients supports this) or is it high intrathoracic pressures related to lower airways obstruction as suggested by Flume?[156] – pneumothorax has not been described before 4 years of age. Given that many very young children had advanced lung disease early in life in past decades, the association of pneumothorax with patients who have survived these initial years suggests that the inflammation and fibrosis after many years of CF lung disease sets the stage for the development of pneumothorax. However Flume has shown that the median age at pneumothorax has not paralleled the increased longevity of CF patients.[156] In two of our patients pneumothorax occurred when they were already considered to be in a terminal state (ages almost 10 and almost 16 years). The other heralded a rapid decline in the lung function of a 17 year old boy. At the time of his first pneumothorax his FEV_1 was 65% of expected. He died in respiratory failure in his 22nd year. This pattern is consistent with the literature which associates the arrival of pneumothorax with a grim prognosis. Analysing all reports to 2002, Flume calculated an overall incidence of 6,4% for pneumothorax in CF.[156] The low incidence of pneumothorax in this population is probably related to limited numbers who have survived or been followed to late adolescence, after which half of all pneumothoraces occur.

Massive haemoptysis has only been seen in one teenager who was 16 years old at its onset. His course is described in the Surgery in CF chapter as he required repeated bronchial artery embolisation.

The single case of empyema is unusual. It occurred at an age well beyond infancy, when CF-associated empyema used to occur. It was sterile, perhaps related to prior antibiotic

therapy. This right-sided empyema and the underlying lung disease led to surgery that is described in the next chapter on Surgery in CF.

In all, 42 patients have died beyond the age of 5 years yet only 11 have had signs of cor pulmonale. Six of the deaths occurred after the patients had been referred to GSH. Details of their terminal disease was not available for study. Right heart failure is notoriously difficult to diagnose in CF. The marked hyperinflation of the lungs and distortion of intrathoracic anatomy owing to fibrosis and atelectasis make ECG and echocardiography very difficult to interpret. Invasive cardiac procedures are rarely indicated in CF therefore clinical signs are needed to make a confident diagnosis of right heart failure. In our experience management of cor pulmonale in CF has been relatively simple with the use of domiciliary oxygen therapy and diuretics. Right heart failure can be postponed by the prevention of nocturnal hypoxaemia with oxygen therapy during sleep. In recent years, staff at the CF clinic have become alert to the need to consider oxygen therapy before heart disease is suspected clinically. Pulse oximetry has become routine in patients with severe lung disease.

The oedema/anaemia complex has been discussed in the section on the presentation of CF. No cases appeared after the diagnosis of CF was made, illustrating that nutritional therapy and PERT resolve this manifestation of CF. One other child from very adverse social circumstances developed nutritional oedema at the age of 4 years. The negative protein balance of poorly managed CF will have played a part in this presentation but it is not strictly an example of the oedema/anaemia complex. The oedema resolved rapidly when he was placed in institutional care for a few months.

ABPA in CF has been defined using immunological criteria.[187] In CF the presence of *A fumigatus* in sputum is common in the absence of symptoms referable to the microorganism. Likewise radiological and clinical criteria that characterise ABPA in asthma overlap with CF lung disease in the absence of *A fumigatus*. In practice in Cape Town the CF-associated ABPA criteria are too strict to be of clinical use leading to the use of a combination of immunological criteria (including specific antibodies to *A*

fumigatus) and clinical criteria. The clinical setting has usually been of a child with persistent of progressive respiratory disease with prominent wheezing which, over a few weeks, does not respond to aggressive therapy including intravenous antibiotics, bronchodilators and physiotherapy. If, in this setting, immunological evidence of hypersensitivity to *A fumigatus* is found, a course of high dose corticosteroid therapy is commenced. Response is judged clinically, on pulmonary function testing and by a reduction in antibody levels. Thus the 9 cases reported here over 29 years represent those cases in which these steps took place. All cases except one were diagnosed in the second half of the period under study, suggesting increased awareness of the complication. It remains unusual, however.

Two cases merit particular mention. One girl developed ABPA under the age of 5 years. Severe lower airways obstruction was a persistent feature. While she responded well immunologically to corticosteroid therapy, reductions in dosage led to recrudescences in antibody levels and symptoms. She died in her 6th year, ABPA and possibly steroid side effects, being significant in her deterioration. The second case did not fit our criteria for ABPA yet *A fumigatus* seemed to play a significant part in his declining lung function. Marked progressive lower airways obstruction developed in the presence of *A fumigatus*. No other organism was consistently grown from his sputum though he was colonised by *P aeruginosa*. He had normal antibody levels to *A fumigatus*. Total IgE levels were also normal. Corticosteroid therapy produced a limited response. Treatment with the antifungal drug, itraconazole, produced some amelioration that was not sustained when the drug was withdrawn. Concerns about toxicity of the drug limited its use. He died in his 9th year with marked peripheral airways obstruction but limited radiological evidence of destructive lung disease.

Summer in the Western Cape province is hot and dry. Persons at risk of heat prostration such as those with CF need to take extra salt to prevent this complication. Such advice is a routine part of the care of children with CF in Cape Town. Of the 8 patients with hyponatraemic dehydration in this CF population, only 2 developed the complication after the diagnosis of CF had been made. The other 6 are those identified in Study 4.1.

One of the two patients had recurrent bouts of salt depletion in her early years; the other, who lived in Wellington, one of the hottest parts of the Western Cape province, had one episode at the age of 4 years which required admission but was able to prevent any recurrences.

All long term health conditions may produce severe psychological morbidity and CF is no exception. Care must include anticipatory guidance and an awareness of this predisposition. Depression is a severe condition in which lack of interest in life, low mood, disrupted sleeping patterns and negative and possibly suicidal ideation occur. In the context of CF, this can have severe repercussions on the child's health status. Eating is often poor and attention to self care declines. While there are specific psychiatric criteria for the diagnosis of depression, the criteria used here could not make use of them because of the retrospective study design. Involvement of mental health specialists was used as a proxy for the diagnosis, meaning that at least the most severe cases were counted. All were adolescents. This is not surprising given that psychological morbidity is more likely in this age group generally. Specifically in CF this is the period when the prognostic and social implications of the disease begin to be fully recognised by the young person. However this does not mean that depression did not occur in younger children. It may not have been recognised or may have been managed within the confines of the family and/or the school. The 5 cases out of 181 reported here should be seen as the minimum incidence of this complication. Given the severe implications for the child's health, psychiatric morbidity in our CF population needs more active investigation. A social worker is a key team member in this endeavour.

It is important to note that, although only three non-surgical, non-anaesthetic-associated complications of therapy were recorded in this study, other may have been missed. Repeated courses of aminoglycoside antibiotics are a risk factor for auditory nerve damage. Only one child had formal testing for this. No cases of fibrosing colonopathy as described as a consequence of PERT have occurred. Of the high-lipase forms of PERT, only Creon High Lipase has been used in this service. Since the first cases of fibrosing colonopathy were reported in 1994, every attempt has been made to keep lipase doses

below 10 000 IU/kg. Most children with CF spent many days in hospital and thus were at risk for nosocomial infections. It is likely that these (and relatively minor complications such as drip-site sepsis) may have been overlooked or not recorded in the notes. Antibiotic sensitivity was apparently only seen once. Other significant episodes are unlikely to have been missed. In adult CF care, it represents a significant factor in the complexity of the management of pulmonary exacerbations.

One male adolescent suffered severe back pain related to kyphosis and microfractures secondary to osteoporosis. He required frequent admissions and the pain made chest physiotherapy difficult. Intensive vitamin and calcium therapy was given but is unlikely to have made a significant difference to his bone mineral density (BMD). Formal study of BMD in our population has been contemplated but not undertaken. One child had BMD measured in private practice and it was low but there were concerns regarding the calibration of equipment usually used for adults. Treatment of osteoporosis with hormonal therapies is difficult and so far untested in children with CF, so prevention remains the key to reducing morbidity in older patients with CF. We demonstrated a low average calcium intake in our population enabling us to intervene in one factor that contributes to osteoporosis in CF.[184] While 25-OH-cholcalciferol and alkaline phosphatase levels were normal in our population, recent evidence suggests that this does not adequately exclude vitamin D deficiency in CF.[207] It is known that winter at the latitude of Cape Town leads to potentially inadequate ultraviolet radiation[208] so it is possible that our patients are mildly deficient in Vitamin D during this season. Further data on vitamin D metabolism in CF from the northern hemisphere are awaited. Optimising nutritional status is the other key to achieving maximum BMD. A more aggressive approach to this has been introduced at the RCCH as the frequent use of gastrostomy feeding attests to (See Chapter 5).

Three children showed features of peptic ulcer disease. Only one had a persistent problem, eventually leading to vagotomy and antrectomy in the era before the role of *Helicobacter pylori* in the pathogenesis of ulcers had been shown (see Chapter 5 p155).

In conclusion, then, it appears that CF as a clinical entity as seen in children and adolescents in the Western Cape province is comparable with other centres in the world. For reasons that require investigation, only the anaemia/oedema complex appears to be more common than elsewhere and only in coloured children. This chapter has illustrated the complexity of CF and its many complications. Only one in three children is destined to have disease that confines itself to PI and lung disease and those problems are burdensome enough. Most children will suffer additional complications of their disease at some time in their formative years. As this chapter and the following clinical chapters illustrate, a broad range of expert services is required to deal with the myriad facets of this disease.

CHAPTER 5

SURGERY IN CYSTIC FIBROSIS

OUTLINE OF CHAPTER

The previous chapter described the clinical manifestations of CF encountered in this population of children and young people with the disease from the Western Cape province. As described there, a number of the features and complications of the disease require surgical interventions. This chapter details the surgical histories of these patients from 1972 to the present day and presents the overall contribution of surgical expertise to the total management over many years of children and adolescents who have CF. After an introduction, a published study covering the 20 years from 1972 is presented. This followed by an update including a recently published letter on the subject of splenectomy in CF.

INTRODUCTION

Exploration of the surgical histories of our patients constituted the means by which I rapidly enlarged my knowledge and understanding of CF. The folder reviews and literature search that were required for this study served as an invaluable boost to my understanding of CF, its true complexities and its range of challenges that, 10 years later, are being presented in this thesis.

The full multisystem nature of the disease is represented in the range of surgical procedures undergone by a significant proportion of CF patients. The gastrointestinal tract (GIT) is the focus of much of the major surgery associated with CF with meconium ileus (MI) and its complications being responsible for the bulk of this.[209] Intestinal obstruction is often a feature of life with CF beyond the neonatal period. Surgery may be

required to relieve this.[172] Pathological gastro-oesophageal reflux (GOR) may necessitate anti-reflux procedures in certain cases.[210] The lung, though the focus of much of the morbidity associated with CF, less commonly demands surgical intervention. However, lobectomies for localised bronchiectasis, intercostal drain insertion and pleural procedures for pneumothoraces, interventional radiology for massive haemoptysis and bronchoscopy for diagnostic and therapeutic purposes are not uncommon.[154] In some countries lung transplantation is a major surgical intervention in patients with CF.[25] Liver disease also has its surgical consequences. Procedures for the management of portal hypertension such as injection sclerotherapy, band ligation of oesophageal varices or porto-systemic shunts may be required.[211] Biliary surgery may be needed for obstructive and infective complications. Liver transplant is also now an established mode of therapy for intractable liver disease in CF.[211] For the Ear, Nose and Throat (ENT) surgeon, there are the problematic nasal polyps and persistent nasal sinus symptoms to be dealt with using procedures such as polypectomy and ethmoidectomy.[212] Enteral feeding with gastrostomy tube placement was introduced in the late 1980s to optimise nutritional status in selected patients with CF.[213] Likewise placement of central and peripheral venous catheters has been regularly performed to reduce the recurrent discomfort associated with the regular intravenous antibiotic therapy that a more vigorous approach to pulmonary infections requires.[214]

The stimulus to the first study reported in this chapter was the management of a young girl who had persistent right iliac fossa pain associated with a mass. Senior doctors in the clinic decided she had to have an exploratory laparotomy. (Her case, being somewhat unusual, is written up fully on p150.) My feeling of great ignorance as to the reasoning and pathology that had led to this decision encouraged me to explore the indications for surgery in patients with CF. My co-workers, Dr J Ireland and Prof M Bowie, helped me with the task of protocol development and collating and distilling the vast range of disease and interventions I uncovered in this retrospective study of 20 years-worth of surgery in CF patients at the RCCH.

The study was published (after getting lost in the editorial offices for some considerable time) by the *South African Journal of Surgery* in 1997.[51] It was accompanied by an editorial by Prof Sam Moore of TBH's Department of Paediatric Surgery on the subject of 'Surgery and Cystic Fibrosis'.[215] This paper in reproduced here as Study 5.1. **References are included at the end of the paper.**

Following the presentation of this article, the surgical experience in the decade following the end of that study period is presented and the full 30 years commented upon in the light of international experience with surgery in CF patients.

STUDY 5.1

Surgery in cystic fibrosis – a 20-year review

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South African Journal of Surgery 1997;35:181-184

ABSTRACT

The surgical histories of 111 patients with cystic fibrosis (CF) seen between 1972 and 1991 were examined. Fifty seven of these children underwent 154 operations and in 34 the surgery was directly related to CF accounting for 84 operations. Meconium ileus and its complications were responsible for 26 of the 32 major abdominal CF-related procedures and there were 3 major CF-related thoracic operations. Only 1 child died within a month of operation. Complications occurred in 11,9% of general anaesthetics and post-operative complications in 9,2% of operations. Patients with CF are likely to need operative intervention and when indicated surgery should have a low morbidity and mortality.

Cystic fibrosis (CF) is a multisystem disorder resulting from a genetic abnormality of the transport of chloride ions across apical membranes of epithelial cells. The brunt of the complications of this defect is borne by the respiratory and gastrointestinal systems. Therapy is largely medical with prevention and treatment of pulmonary infections and pancreatic enzyme replacement being the mainstay. The disease process may demand surgical intervention for diagnostic or therapeutic reasons.[1] This can begin in the neonatal period with meconium ileus (MI)[2] and, at an advanced stage of the disease, heart-lung transplantation is now a possibility.[3] The effects of respiratory complications such as bronchiectasis and pneumothorax in some instances can be ameliorated with surgical techniques.[4,5] Laparotomy is often indicated when abdominal complications such as intussusception occur.[6] Exploratory laparotomy may be indicated when abdominal pain or masses cause diagnostic uncertainty.[2] The associated lung disease increases the anaesthetic risk especially in the later stages of the disease.[7]

As surgery is likely to play a significant role in the overall management of CF we reviewed the surgical histories of our patients to document 1) the number and types of surgical procedures undertaken, 2) the indications and outcomes and 3) the risks of surgery.

PATIENTS AND METHODS

The hospital records of all CF patients who had been seen at the Red Cross War Memorial Children's Hospital were examined. CF had been diagnosed on clinical features or family history and confirmed by a positive sweat test. Details recorded included gender, ethnic group, presenting symptoms and, where known, genetic status. Children who had only been seen for confirmation of the diagnosis and those in whom the diagnosis was made *post-mortem* were excluded.

All diagnostic and therapeutic procedures requiring anaesthesia or sedation performed on this group of children in the 20 year period from January 1972 to December 1991 were recorded and classified into 3 groups:

GROUP 1:	Major procedures related to CF
GROUP 2:	Minor procedures related to CF
GROUP 3:	Procedures unrelated to CF

For Group 1, indications were defined based on experience and a literature review prior to retrieval of the data and were recorded as in the preoperative assessment regardless of the surgical findings (see Box 5.1). Outcomes were defined as good, ineffective or bad using criteria related to the indication. For Groups 2 and 3 the type of procedure alone was recorded.

BOX 5.1

	INDICATIONS	OUTCOME		
	ABDOMINAL SURGERY			
		Good	Ineffective	Bad
A)	Persistent abdominal pain with focal RLQ tenderness not responsive to medical therapy	Removal of symptoms that indicated surgery; physician's statement	Continuing symptoms; physician's statement	Aggravation-of symptoms; clinician's statement
B)	Persistent abdominal pain suggestive of DIOS inadequately responsive to bowel clearing procedures and other medical therapy with demonstrable ileocaecal faecal retention			death related to operation; complication worsening status
C)	Caecal or other bowel-related mass unresponsive to bowel clearing procedures and symptomatic			
D)	Bowel obstruction, except demonstrable intussusception, not responding to conservative measures			
E)	Intussusception not responsive to enema therapy			
F)	Meconium ileus unresponsive to enema therapy			
G)	Complicated meconium ileus			
H)	Persistent abdominal pain due to disease of the biliary tree			
I)	Uncontrolled bleeding oesophageal varices			
J)	Persistent symptomatic GOR			
K)	Acute abdomen, peritonitis			
L)	Typical acute appendicitis			

CHEST SURGERY

M)	Severe localised chest pathology with no improvement or shortlived improvement in respiratory symptoms after vigorous medical therapy	Fewer chest infections than in the year before	As many infections	See above
N)	Progressive scoliosis due to localised lung or pleural fibrosis	Reduction in scoliosis	Unchanged	
O)	Recurrent and/or persistent pneumothorax	No pneumothorax	Recurrence	
P)	Empyema not completely responsive to thoracocentesis and medical measures	Clearing of empyema	Not cleared	
Q)	Life threatening or severe recurrent haemoptysis	No further haemoptysis	Ongoing haemoptysis	
R)	Rapidly declining respiratory function and severe focal chest pathology	Improvement in clinical respiratory state	No arrest or slowing of decline	

For all groups anaesthetic complications (see Box 5.2) were described as being related or unrelated to CF as defined by Lamberty and Rubin.[7] Complications due to the surgery were recorded separately. Only complications related to operations carried out at our hospital were recorded.

BOX 5.2

ANAESTHETIC COMPLICATIONS

COMPLICATIONS RELATED TO CF

A) Difficult induction

B) Excessive coughing and secretions

C) Difficult intubation because of secretions

D) Difficulty with ventilation

E) Difficulty maintaining anaesthesia

F) Secretions causing airway obstruction

G) Unstable blood sugar

H) Haemoptysis

RESULTS

One hundred and thirteen patients with CF fulfilled the criteria for inclusion in the study. The records of 2 were missing. Fifty seven of the remaining 111 patients had undergone at least one procedure. There was no difference between those who had had surgery and those who had not with respect to gender, ethnic group, delta F508 mutation status or symptoms at initial presentation analysed by organ system.

One hundred and fifty four procedures were carried out on the 57 patients in the 20 year period (Table I). The maximum number of operations per child was 14. Twenty three patients had 1 operation, 12 had 2, 7 had 3 and 10 had 4. Five patients underwent 5 or more operations. The median age at operation was 4 years (Range 0-24 years).

TABLE I: TYPES OF OPERATION

	GROUP		
	1	2	3
Abdominal	32	34	18
Chest	3	8	1
ENT	0	6	30
Other	0	1	21
Total(N=154)	35	49	70

36 (23,3%) operations were done elsewhere (Group1 - 10, Group 2 - 4, Group 3 - 22).

Operations related to CF

Thirty four (30,6%) of the 111 patients underwent an operation related to CF. Eighty four (54,5%) operations were related to CF (Table I). Indications and outcomes for major surgery are shown in Table II. Ten operations done at other hospitals are not included in the Table as indications for surgery were not available to us. These were all laparotomies and 8 were related to MI.

TABLE II: MAJOR OPERATIONS RELATED TO CYSTIC FIBROSIS

INDICATION	PATIENT NUMBER	AGE AT OPERATION (yrs:mths)	OPERATION
Abdominal mass[6,15]	1	6:0	Incision and drainage of abdominal wall abscess
Bowel obstruction obstruction. not responding to conservative measures[2 6]	2	0:11	Previous MI surgery. Adhesive bowel segment of bowel resected
	3	Neonate	Jejunal atresia. Microcolon with meconium plugs. Santulli procedure
	4	1:9	Previous MI surgery and laparotomy for adhesions. Severe adhesions. Pseudo-membranous colitis. Ileostomy. Wound sepsis. Died after re-exploration of the wound.
	5	2:3	Previous MI surgery. Adhesive bowel obstruction. Adhesions divided.
	6	0:3	Closure of colostomy followed by torsion at site due to adhesions. Previous complicated MI. Bowel resection.
Acute abdomen	7	10:0	Perforated appendicitis with peritonitis. Appendicectomy
	8	8:9	Terminal ileitis with haemorrhagic lymph nodes. Free peritoneal fluid grew α-haemolytic streptococcus. Appendix showed chronic inflammatory cells. Responded to peritoneal lavage and antibiotics.
MI, failed enema(s)	5, 9-16	Neonates	Various. See Ref 21.
Complicated MI	17	Neonate	Perforation of splenic flexure with meconium peritonitis. Colostomy.
	6	Neonate	Proximal volvulus with atresia, meconium peritonitis and pseudocyst. Ileostomy.
	18	Neonate	Mid ileal volvulus with peritonitis. Resection and ileostomy.
Persistent symptom-atic GOR* 2	19	1:6	Nissen Fundoplication.
	9	2:6	Right upper lobectomy.
Focal lung disease, repeated infections4	20	3:6	Right pneumonectomy.
	21	5:6	Right decortication following empyema and pneumonia.

*GOR = gastro-oesophageal reflux

Minor procedures undertaken are shown in Table III.

TABLE III

MINOR OPERATIONS RELATED TO CYSTIC FIBROSIS

	Operation	Number (N=49)
Abdominal	Endoscopy/Sclerotherapy	21
	Closure of Stoma	11
	Rectal Prolapse	2
Chest	Insertion ICD*	5
	Bronchoscopy	3
ENT	Polypectomy	2
	Polypectomy/Ethmoidectomy	3
	Examination under anaesthetic	1
Other	Exploration of suture line	1

*ICD = Intercostal drain

Operations unrelated to CF

Seventy operations fell into this category (Table I). The majority of this surgery was minor. ENT operations predominate. Thirteen of the 18 abdominal procedures were endoscopies performed on one patient for a chronic duodenal ulcer. (These endoscopies were classified as unrelated to CF owing to the uncertainty about the relationship between peptic ulcer disease and CF.[8])

Complications

One hundred and nine general anaesthetics (GA) were carried out at our hospital. There were 13 (11,9%) complications. Eight related to CF were bronchospasm(3), laryngospasm(2), a difficult induction owing to secretions, a small haemoptysis and one child was difficult to keep anaesthetised. There were 2 minor epistaxes, one brief apnoea, an urticarial reaction to alcuronium and one child became dehydrated when a drip disconnected. None of these complications produced more than shortlived morbidity.

Seven procedures were performed with local anaesthesia and 2 under sedation. No complications were encountered.

Post-operative complications occurred with 11 (9,2%) operations. Infections accounted for 7 of these (chest infection 3, wound sepsis 3, nosocomial enteritis 1). Torsion of bowel at the ileostomy site was the only early non-infective complication of MI surgery (but one child developed bowel obstruction due to adhesions and meconium plugs 3 days after closure of ileostomy (Patient 7 Table II) and surgical emphysema affected one of the thoracotomy cases. One child developed a stricture following repeated injection sclerotherapy for oesophageal varices.

DISCUSSION

Since the first delineation of the variable course of CF by Shwachman and Kulczycki,[9] the need for surgical intervention to relieve some of its symptoms and complications has been recognised.[10 11] In subsequent decades this has been amply attested to with heart-lung transplant being the latest regularly performed procedure.[3] Despite the multiplicity of operations demanded by the complications of CF there are few reports of the extent of surgical intervention and morbidity in CF populations. Most reports relate to a single system or disease process. Olsen *et al*[12] report a 15 year experience at one hospital but operations before diagnosis and those performed at other hospitals are not included. Three studies over 3 decades describe surgical experience in CF from the anaesthetist's perspective.[7 13 14] Gastrointestinal surgery over a 10 year period is presented by Gross *et al*,[2] appendix surgery over 24 years by Coughlin *et al*[15] and there is a number of series covering pulmonary resection.[4 16 17] Ear, nose and throat (ENT) surgery over 2 decades is presented by Reilly *et al*.[18]

In this study the total surgical burden experienced by a CF population over 2 decades is presented. Half of our CF population underwent at least one surgical procedure. The majority (54,5%) of surgery was related to the disease and was carried out on 30,6% of the patients.

The extent of surgery due to the disease is higher than this as some procedures were undertaken before the diagnosis of CF was established (a liver arteriogram and a small bowel biopsy) and another was the result of complications of CF therapy (eg. oesophageal stenosis after sclerotherapy). Although classified as 'unrelated' many of the adenotonsillectomies, grommet insertions and sinus washouts were done prior to diagnosis presumably for chronic respiratory tract symptoms. Maw[19] states that such operations for CF-related symptoms are of questionable benefit. In our study they represent 14,6% of the total. Early diagnosis could significantly decrease the amount of surgery CF patients undergo.

Abdominal surgery dominates the CF-related interventions. Sixty six of the 81 related operations were abdominal and of the major procedures in this group those related to MI form the bulk (27/32).

Intestinal obstruction, abdominal pain and right lower quadrant masses frequently cause diagnostic difficulty in CF patients. The distal intestinal obstruction syndrome (DIOS) is the commonest entity responsible but intussusception, appendiceal pathology, Crohn's disease or biliary tract disease may occur with overlapping symptoms, signs and results on investigation. In all, 4,5% of our cohort had surgery for these indications. In a 10 year period Gross *et al*[2] operated on 6/189 patients (cholecystectomy 3, DIOS 2, intussusception 1). Olsen *et al*[12] reports 36 such operations in 210 patients in 15 years. This higher rate reflects an older CF population.

The small number of pulmonary resections (2,7%) accords with recent experience in larger centres. Steinkamp *et al*[16] report 3 out of 160 patients undergoing lobectomies for localised bronchiectasis. It is well established that with careful selection pulmonary resection in CF can have an excellent effect on a patient's well-being[4] and both our children have enjoyed much better health following surgery. Empyema is an uncommon problem in CF. No organism was isolated in the child reported and he did well postoperatively and remains so 4 years on.

Postoperative complications were for the most part minor and transitory. The most serious (bowel torsion, adhesive intestinal obstruction) related to MI surgery but the introduction of T-tube ileostomy has prevented these in recent years.[20] Only 3 patients had a chest infection within a week of surgery. Atelectasis and respiratory failure, both features of earlier series,[13 14] did not occur probably reflecting the improved pulmonary status of children with CF in recent years as well as advances in management.[7] Morbidity was higher than that reported by Olsen *et al*[12] (9,2% vs 3%) but nasal polypectomies and central intravenous line insertions, both procedures with low morbidities, constituted almost half of their operations.

The nutritional and respiratory effects of CF potentially make administration of GAs problematic.[7] Ventilation/perfusion mismatch, airway reactivity and secretions demand careful management in the perioperative period. The anaesthetic complications seen here (11,9%) compare well with those reported from a centre in which much more CF surgery is performed (13,4%).[7] In a young population such as ours, morbidity will be lower because lung disease is less advanced but the use of GA is high as sedation or regional anaesthesia present problems in young children. Concerns expressed about the long term effect of GA on lung function patients with CF[21] have not been addressed by this study but we have not noted a difference in disease status between those who had surgery and those who did not.

CONCLUSIONS

In this study, the total surgical burden experienced by a CF population is reported. It is important to note that this is a relatively young population and that some surgically important complications of the disease appear mainly in late adolescence and adulthood. Yet the experience shows that half of our patients had surgery. The disease itself is responsible for over half of the procedures with MI-related operations forming a significant proportion. Given the right indications a good outcome with limited morbidity can be expected. The number of operations and thus morbidity could be reduced by early recognition of CF and will probably continue to diminish with advances in medical and surgical management.

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UPDATE AND COMMENTARY

Apart from teaching me a great deal about CF, this study remains unique in its comprehensive view of surgery in CF. However, as shown in the discussion in the article, the proportion of surgical procedures in CF varies between centres e.g. the virtual absence of central venous line placement in Cape Town and its high usage in North American studies. Access to lung transplantation would constitute another difference. Over time practice changes: advances are made; fads are shown to be just that. The use of Intralipid and other forms of parenteral nutrition was all the rage in the 1970s[216] but their use passed once effective PERT and high fat diets reversed much of the malnutrition seen in CF. Even within the two decades of our small study the complication rate of MI surgery diminished. This fact was noted by Moore in the editorial that accompanied our article.[215]

It is now 12 years since the procedures entered into this study were performed. Have changes in clinical practice in Cape Town changed the frequency or the pattern of surgery

in this population? We predicted a diminution of the surgical burden with the earlier diagnosis of CF and advances in treatment. Has this taken place?

Using the same methodology as the study reported in the *SAJS*, experience from January 1992 to August 2003 (the end of the study period for the population described in Chapters 2 and 3) was reviewed. The number and range of procedures are shown in Tables 5.1 and 5.2. In all, 59 patients underwent 128 surgical procedures, 21 patients having had earlier procedures that were included in the first study. Sixty eight of the 128 procedures (53%) were performed at the RCCH.

Table 5.1 Operations performed from January 1992 to August 2003

	Group		
	1	**2**	**3**
Abdominal	27	37	4
Chest	3	6	0
ENT	0	10	17
Other	0	6	8
TOTAL (N = 128)	**30**	**69**	**29**

Table 5.2 Operations related to cystic fibrosis performed between January 1992 and August 2003

	Operations related to Cystic Fibrosis			
MAJOR	Abdominal	MI Surgery	11	
		Laparotomy	7	See text & Table 5.3 for details
		Vagotomy/antrectomy	1	See text & Table 5.3 for details
		Anti-reflux procedure	8	3 with gastrostomy See text & Table 5.3 for details
	Chest	Lobectomy	1	See text for details
		Bronchial artery embolisation	2	See text for details
MINOR	Abdominal	Endoscopy ± sclerotherapy	16	
		PEG insertion	10	
		PEG replacement	8	
		PEG removal	3	
	Chest	Intercostal drain insertion	1	
		Bronchoscopy	4	
		Thoracoscopy	1	
	ENT	Polypectomy	10	
	Other	Venous lines	6	

PEG – percutaneous endoscopic gastrostomy
ENT – ear, nose and throat

Abdominal Surgery

Of the 9 MI-related operations since 1992 only two took place at the RCCH. Five were performed in private hospitals and two at TBH. Only one child born in the last 11 years developed a complication related to MI surgery (adhesive bowel obstruction at 6 months of age in 2003. See Table 5.3). There has been no mortality from MI. The excellent outlook for MI in Cape Town continues. The surgery that took place in private hospitals was all performed by paediatric surgeons affiliated to Cape Town's two tertiary public paediatric centres.

In the period covered by the first study, MI-related surgery made up the bulk of major abdominal surgery in CF (26/34 procedures). Things have changed: between 1992 and 2003 only 12 of the 27 major abdominal operations were related to MI. Changes in

operative technique have removed stoma closure from the list of procedures. Two of the major operations were for volvuli in two girls whose initial MI surgery took place years before in the period covered by the first study. These and the other major abdominal surgery and its indications and outcomes are shown in Table 5.3.

Table 5.3 Major abdominal surgery in cystic fibrosis excluding that done for meconium ileus

Indication	Age at operation (yrs:mths)	Operation	Outcome
Abdominal mass	6:3	Removal of mucocoele of the appendix (see text)	Good
	14:1	Splenectomy (see text)	Good
Bowel obstruction not responding to conservative measures	0:6	Adhesive bowel obstruction following MI surgery. Division of adhesions	Good
	2:0	Volvulus in child with previous MI surgery	Good
	17:1	Volvulus in adolescent with previous MI surgery.	Good
Persistent peptic ulcer disease	16:8	Vagotomy and antrectomy	Good
Persistent GOR with symptoms (see text)	0:5	Nissan soon after CF diagnosis	Good
	0:5	Nissan soon after CF diagnosis	Fair (see line below)
	1:5	Re-do with repair of paraoesophageal hernia	Good
	0.5	Nissan & gastrostomy after CF diagnosis	Good
	0:4	Nissan before CF diagnosis	Good
	9:1	Abdominal pain with anorexia. Nissan and gastrostomy	Good
	16:4	Heart burn and anorexia. Nissan and gastrostomy	Good
	1:8	Boix-Achoa procedure performed before CF diagnosis made	Bad (see line below)
Bleeding after Boix-Achoa procedure	1:8	Laparotomy to tie off bleeding artery	Good

MI – meconium ileus
CF – cystic fibrosis

Surgery for GOR in CF has changed considerably between the two periods under review. In the first period only one operation for GOR was performed. In the last 11 years, 8 such operations have been carried out (Tables 5.2 and 5.3). Two of the 8 procedures

were done for persistent chest symptoms before the diagnosis of CF was made but the other 6 were done after the diagnosis. The potentially lethal combination of the tendency of CF to produce severe chest disease in some infants and severe GOR which has a higher prevalence in CF led to early anti-reflux procedures in three infants. In all three there was considerable consequent reduction in the respiratory symptomatology. All three are now healthy young children with minimal pulmonary disease. One of these infants presented with dysphagia a year after the anti-reflux procedure having developed a paraoesophageal hernia. Surgery to repair this and to re-do the wrap was successful.

In contrast to the respiratory indication for GOR surgery in infants, two older boys required procedures for GOR because of severe gastrointestinal symptoms: abdominal pain and heart burn. In both patients GOR was worsening nutritional status, and the opportunity to insert a gastrostomy button during surgery was taken to allow supplemental feeding. Both boys responded well to these interventions.

Three patients who underwent three other major abdominal procedures warrant special mention.

Case 1: Right lower quadrant mass

This female CF patient had presented in infancy with failure to thrive and recurrent chest infections. She had PI and had been placed on PERT. She had had an uncomplicated course until the age of 5 and a half years apart from a single episode of painless rectal bleeding. She was then noted to have a right iliac fossa (RIF) mass which was thought to be due to faeces. This persisted and enlarged. Clearance was attempted with balanced polyethylene glycol/electrolyte solution to no effect. Ultrasound confirmed the presence of the mass but did not help characterise it. Abdominal CT scan suggested an ileocolic intussusception but was not diagnostic. A laparotomy was undertaken. Inspissated faeces were found in the appendix and caecum. Appendicectomy was performed with evacuation of faeces through a caecostomy. Histology showed an appendix distended with mucin with focal cryptitis and increased numbers of polymorphs in the lamina propria.

In the months following the operation she remained well but there was still a vague mass palpable in the RIF. There was occasional pain localised to this area. With time the mass became more prominent and further oral attempts at bowel clearance were made with partial success.

Nine months after the operation she began to lose her appetite, complained of satiety and over two months she lost 3 kg in weight. She had intermittent cramping abdominal pain and episodes of fever. Chest X-ray and sputum culture were clear. Urine microscopy and culture were normal. She had a white cell count of $13{,}5x10^9/l$ with a neutrophil predominance. Electrolytes, urea and creatinine were normal but her serum albumin level was 30 g/dl. ESR was 121 mm/hr.

Abdominal X-ray suggested a mass in the RIF and a few small air/fluid levels in the small bowel. Ultrasound showed marked thickening of the terminal ileum and ascending colon walls and mucosa. There were several enlarged mesenteric lymph nodes in the RIF and paracaval regions with a small amount of fluid in the Pouch of Douglas. Contrast CT of the abdomen with Gastrografin® showed delayed bowel transit with an irregular narrow track of contrast passing through thickened terminal ileum, caecum and ascending colon.

Colonoscopy was performed. This showed ulceration and granulomatous inflammation in the ascending colon. There were thick adherent secretions in the lumen of the bowel. The rest of the colon appeared to be normal. Radioisotope scanning with Gallium^{67} showed a large irregular area of increased uptake extending across the abdomen from the RIF towards the left costal margin suggesting diffuse small bowel inflammation. *Yersinia* antibodies and culture of tissue from the caecum were negative. Tests for TB were also negative.

She was treated with broad spectrum antibiotics, initially for two weeks. However over the following three months symptoms recurred frequently, only settling (and often

incompletely) when further antibiotic courses were given. During this time she developed swollen painful ankles. Intermittent abdominal pain continued, often associated with fever and raised ESR level; the RIF mass remained palpable. It was decided to treat her as if she had Crohn's disease. Prednisone therapy brought about an immediate cessation of pain and reduction in the size of the mass. Sulphasalazine was added enabling the steroid dose to the reduced and then stopped. The symptoms did not return. The anti-inflammatory medication was continued until she was 16 years old. Symptoms had not recurred by the end of the study period when she was 17 years and nine months old.

Lloyd Still from Chicago has taken a special interest in Crohn's Disease in the context of CF. He reviewed the literature in 1994, identifying 12 reported cases, 33% of whom had arthritis.[173] Seventy five percent had fistulae, a complication our patient was spared. His survey of CF centres revealed 28 cases of inflammatory bowel disease, 25 of which were Crohn's disease. One out of every 404 CF cases had inflammatory bowel disease; it is not a common complication of CF but is more common in CF than in the general population. Most cases were associated, as in our case, with DIOS. The diagnosis of Crohn's disease depends on clinical, radiographic and histologic features. These this patient had and, together with the gratifying response to anti-inflammatory therapy, they make a convincing case for Crohn's disease.

Case 2: Massive splenomegaly

This case was described in a letter we wrote to the *Archives of Diseases in Childhood* that was published in November 2004.[217] In 2003 the journal had published a paper by Thalhammer and colleagues describing three CF patients who had undergone partial splenectomy.[218] The first patients had his spleen partially removed for hypersplenism and abdominal discomfort; the second for severe abdominal pain; and the third for pain and increasing dyspnoea. The authors discussed the risks of this procedure. Increased suspectibility to infection was the main concern. One of their patients required re-laparotomy for intra-abdominal bleeding and they quoted a previous paper that described problematic post operative complications of splenectomy in 3 out of 6 patients. These

risks led to a Commentary that accompanied Thalhammer and colleagues' paper. Kelly and de Ville de Goyet were

> .....doubtful that this operation [could] be justified in patients with cystic fibrosis in view of modern methods for controlling portal hypertension.....[219]

This commentary drew two letters to the *Archives*, one from the authors of the original report and another from the group whose work they had quoted defending splenectomy.[220 221] It was into this ferment that we made our contribution, based on our experience.

Arch Dis Child 2004;89:1078

Dear Sir

Re: Splenectomy in cystic fibrosis patients

A recent article[1], a commentary[2] and two letters[3 4] in the *Archives of Disease in Childhood* have revealed controversy over the place of partial splenectomy in portal hypertension in cystic fibrosis (CF). We wish to contribute to the debate with a case report:

Our male patient was homozygous for the ΔF508 mutation. He was pancreatic insufficient, his lungs were colonised with *Pseudomonas aeruginosa* from an early age and he had two episodes of allergic bronchopulmonary aspergillosis. When he was 8 years old abdominal ultrasound showed variable echogenicity of the liver compatible with cirrhosis with thick bile in the biliary tree. Treatment with ursodeoxycholic acid was commenced. Recurrent abdominal pain associated with severe gastro-oesophageal reflux led to an anti-reflux procedure being performed when he was 9 years old. A gastrostomy button was placed at the same time for night time supplementary feeding. Cirrhosis of the liver was confirmed intraoperatively. Over the next few years a massive

splenomegaly developed. Full blood count showed features of hypersplenism but he remained asymptomatic with respect to the haematological abnormality. At the age of 13 years he developed severe abdominal pain in the area over the spleen. Oral analgesia was not sufficient to deal with this ongoing pain and he was unable to attend school, exercise or do chest physiotherapy over a number of months. He had 2 episodes of probable melaena. He developed severe, intercurrent shoulder tip pain secondary to diaphragmatic irritation from splenic infarcts. Computerised tomography of the abdomen showed the spleen's span to be 30 cm, with 2 infarcts. Opiates were given to control pain but it proved to be intractable in an otherwise stoical patient. Eventually, because of the risk to his lungs, his poor quality of life and the risk posed to his gastrostomy by the massive spleen, partial splenectomy and possible splenorenal shunting were planned. Pneumococcal vaccine was prescribed. His white cell count (WCC) was $1{,}5x10^9/l$, his platelet count was $58x10^9/l$ and his INR was 1,6. At laparotomy, perisplenitis in the diaphragmatic area necessitated a total splenectomy. Shunting was not undertaken. The spleen weighed 1 834g and there were numerous infarcts. Post operatively he did well, patient-controlled analgesia being used to encourage early mobilisation. Eight days later elective banding of oesophageal varices took place. Follow up endoscopy showed that this had ablated all the vessels. Two years later he no longer has abdominal pain, has not had severe infections, has a normal full blood count (WCC $12.3x10^9/l$, haemoglobin 14.1g/dl, platelets $486x10^9/l$) and has stable lung function.

The debate on the justification for removing all or part of the spleen in patients with CF and portal hypertension hinges on two considerations: indications and risks In their commentary, Kelly and de Ville de Goyet[2] emphasised the risks: infection, compromising future transplantation, while questioning the indications in the cases presented by Thalhammer et al: hypersplenism and discomfort[1]. In their rebuttal, Thalhammer et al[3] emphasise the hypersplenism and not the pain and discomfort described in their case reports. In their accompanying letter, Chazalette and colleagues[4] do not mention pain as an indication. We would agree with Kelly and de Ville de Goyet[2] that hypersplenism in the absence of significant consequences is not on its own an indication for this major procedure (we note the number of re-laparotomies required in these small series) but

would emphasise that quality of life and local effects of the size of the spleen may justify the surgical and immunological risks.

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Case 3: Persistent peptic ulcer disease

The vagotomy and antrectomy indicated in Table 5.3 was performed on a young man with a recurrent and persistent duodenal ulcer. During the period described in our first paper he had had 13 endoscopies related to this ulcer. The 'curative' procedure predated the advent of triple therapy for *Helicobacter pylori* and is unlikely to be performed ever again in a patient with CF! His ulcer was indeed cured by the operation.

The idea of gastrostomy insertion to enhance nutrition in CF was introduced to the RCCH CF team by Dr J Littlewood in 1988. PEG insertion was first used at the hospital in the early 1990s and CF patients were among the first to have the procedure performed. The experience took the form of an accelerated version of international experience. The first two patients to have the procedure were sisters with advanced lung disease. The older sister gained 2 kg in the 11 months before she died; the younger sister gained no weight

in the 8 months before she died. As Levy and colleagues had shown in 1986, such patients are unlikely to receive optimal benefit from enhanced enteral feeding.[213] In their study the patients who died all had severe malnutrition and lung disease, most dying within 0,2 years of the nutritional intervention. Weight gain was not achieved in nearly all of them. Such feeding, in the opinion of the authors, 'is likely to be most beneficial when it is begun early in the development of malnutrition.' Since this lesson has been learnt, 11 patients have had gastrostomies inserted: 3 at the time of anti-reflux surgery and 8 with the PEG technique. Four of the 8 PEG cases were included in an article about PEG experience at RCCH by van der Merwe and colleagues in the *South African Medical Journal*.[222] Interestingly two teenage boys not included in the *SAMJ* report determinedly put on weight by oral means in order to have their gastrostomies removed 5 and 15 months after insertion. The longest period any child had a gastrostomy was 73 months. Apart from the sisters, five other patients have died with their PEGs *in situ*, 16, 22, 28, 55 and 42 months after insertion. All in all 21 procedures involving PEGs (insertion, replacement, removal) were undertaken in the latter period where none were done in the first period. Peri-operative complications were few: two older boys complained of considerable pain in the immediate post-operative period when their PEGS were first inserted. Most children were discharged within two days of the procedure. The PEG has thus proved simple and effective in CF in recent our experience; an advance in the nutritional care of children and adolescents with CF.

Only in the 1990s did a more aggressive approach to the presence of *P aeruginosa* take root in the Clinic, but routine intravenous therapy has never been practised. As shown in Chapter 7, the organism was identified relatively late in this population. This may explain the very low use of implantable devices. The lack of experienced nurses and almost no home care support also led to avoidance of this means of venous access. Percutaneous indwelling catheters have been preferred. This contrasts with practice in well-resourced countries.[214]

Transplantation surgery is undertaken in SA but has not so far been performed on patients from Cape Town. No patient from our service has been offered lung transplantation. The

procedure and the ongoing immunomodulatory management have not been offered by public services in Cape Town. The history in the private sector has not so far been positive. The RCCH CF team has not been recommending that parents follow possible options elsewhere unless they plan to emigrate. Lung transplantation is being practised with increasing success in highly specialised centres in Western countries but requires high levels of staffing and expertise as well as easy access to this expertise for patients.[233] Without these resources, outcomes are dismal. Warner has pointed out the dangers of false expectations being given to families.[224] He noted that good palliative care options may be denied a child because of a perceived chance of rescue by transplantation. The scales in Western countries may be balanced differently now, but, for SA, Warner's words are wisdom itself. Liver transplantation has a much happier pedigree in SA.[225] With most operations performed for biliary atresia and acute liver failure, survival in recent years has exceeded 82%. However no child with CF has had liver disease severe enough to consider transplant assessment.

CONCLUSION

This review has highlighted the need for a multidisciplinary approach to the management of CF. General paediatric surgical expertise as well as that provided by a number of sub-disciplines is required for a significant proportion of CF patients. Together with this, anaesthetic and intensive care expertise needs to be available for optimal treatment of CF patients. Experience at the RCCH has been that good outcomes can be expected with few complications even when major surgery such as lobectomy is performed.

CHAPTER 6

NUTRITIONAL AND GROWTH ASPECTS

OUTLINE OF CHAPTER

This chapter on Nutrition and Growth in CF reports two cross-sectional studies. After a discussion on the development of modern nutritional management of CF and current understanding of energy balance in CF (which is critical to auxology), the first study (Study 6.1) that I undertook is presented. This is a cross-sectional study of nutritional status and energy balance. This is followed by Study 6.2. By comparing the growth of children attending the CF Clinic at the time of Study 6.1 with those who attended 10 years previously, I attempted to put the nutritional status of the children in Study 6.1 into an historical context. These two studies are followed by a commentary that examines the value of the studies, the changes in nutritional care at the RCCH CF Clinic introduced as a result of these studies and recent developments in the CF nutrition literature that impact on the assessment of nutrition and growth in CF in South Africa. Proposals around future areas of study in this field and their methodological considerations complete the chapter.

INTRODUCTION

The development of nutritional treatments in cystic fibrosis

While the malabsorptive aspects of CF led to its delineation as a clinical entity,[1 2] in terms of management and assessment, attention soon turned to its respiratory aspects. The advent of early forms of PERT ameliorated some of the nutritional effects of steatorrhoea. The prognostic significance of nutritional status was recognised by Shwachman in Boston who included an assessment of nutrition in his scoring system.[10]

However it is clear from the following quotation from the paper that proposed this method of assessment that malabsorption was far from being overcome:

> NUTRITION. Moderate grade: .....poorly formed, bulky, fatty offensive stools;.....

Patients reported in this study were "practically all" on pancreatin. In fact to reduce the persistent symptoms of fat malabsorption, *low* fat diets were advocated:

> The treatment aimed at improving nutrition consisted of a liberal diet in which a relatively high protein intake was emphasized (sic), and an effort was made to reduce the total fat intake.

Improvement in nutritional status and prognosis in CF at this time related largely to earlier diagnosis, the advent of better antibiotics and their liberal use and the greater experience of clinic staff.

That attention to improved energy balance by using liberal amounts of fat in the diet would yield better overall outcomes in CF was the thesis that led the Toronto CF Clinic in Canada to adopt this approach to nutrition.[226] In advocating this approach in 1974, Crozier[227] wrote,

> To deprive the child with cystic fibrosis who usually has very little subcutaneous fat of this important nutrient seems ridiculous.

High doses of pancreatic enzyme supplementation were given to maximise fat absorption. Five years later the Toronto group was able to show improved growth to the point of near normal heights and weights of CF patients as a result of this approach. A seminal paper[16] that this group produced comparing patient outcomes between their 'high fat' and Boston's 'low fat' regimes strongly suggested both that high fat diets worked and that careful attention to good nutrition in CF could prolong survival. Patients in Boston were shorter than those in Toronto and from the age of 10 years the survival curves separated with median survival being 21 years in Boston versus 30 years in Toronto. This high fat approach to nutrition in CF took a while to be accepted and even in the mid-1980s some still advocated the low fat approach (Charlotte Anderson, Birmingham CF Clinic, UK in slide-tape presentation 1984, ICH Library, UCT – now deleted).

That the key to optimal growth and thus optimal survival was an adequate (and usually very high [see below]) energy intake led to new standards of care in the nutritional management of CF patients.[228] Energy intake was the watchword. New methods of boosting energy intake, including night time gastrostomy feeding, became the norm in the 1990s.

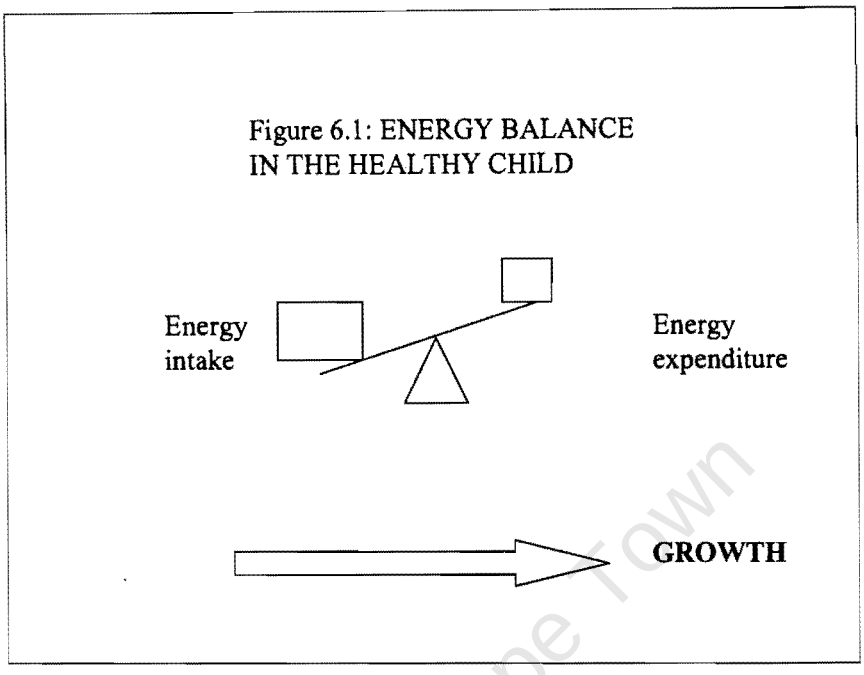
Current understanding of the pathogenesis of growth and nutritional problems in cystic fibrosis

It is a fundamental precept of auxology that the growth of a developing organism can only occur if energy intake exceeds energy expenditure. Genetic growth potential will only be realised if there is a sufficiently positive energy balance to allow optimal growth.

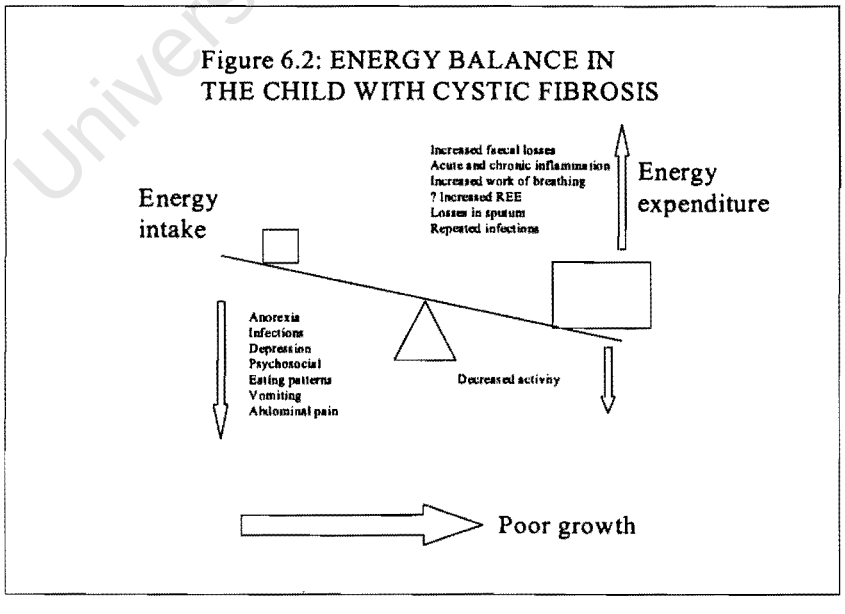
In healthy children energy is expended on

1) Resting energy expenditure (REE): energy used in metabolic (e.g. protein synthesis, ion pumps) and resting mechanical activities (e.g. heart beat and breathing) that are needed to maintain body integrity. This makes up 50-60% of total energy expenditure (TEE);
2) Diet induced thermogenesis (5-8% of TEE).
3) Activities of daily living (30-40% of TEE)
4) Faecal energy losses (vary with dietary energy intake)

Where there is adequate access to food, the healthy child eats enough to account for energy expenditure and what is needed to grow. This energy balance is shown in Figure 6.1.



The child with CF has a more complex energy balance equation.[229] Figure 6.2 shows the balance in a child with CF. In the majority of such children the balance will tend to the negative leading to poor growth unless remedial measures are taken.



Energy expenditure in the child with CF (Figure 6.2):

Increased faecal losses

Pancreatic exocrine gland insufficiency eventually occurs in about 90% of CF cases. This leads to malabsorption and steatorrhoea. Even with modern PERT an average of 11% of dietary fat intake may be lost in the stool. Increased carbohydrate losses in the stool may also occur owing to inadequate colonic salvage secondary to antibiotic effects on colonic flora.[230]

Acute and chronic inflammation

Inflammation consumes energy. In acute exacerbations of pulmonary infections in CF, an vigorous inflammatory response is normal. That this may increase REE has been demonstrated by Steinkamp and colleagues.[231] When assessing 29 patients with an acute pulmonary exacerbation due to *P aeruginosa* they found an average REE of 119% of expected. Twelve patients had no increase in REE. Treatment of the exacerbation with anti-pseudomonal antibiotics decreased measures of inflammation such as white blood cell count and C-reactive protein. The elevated REEs decreased simultaneously. Naon and colleagues were also able to show a decrease in REE during treatment for acute infection in CF.[232] This group were able to show that the magnitude of the decrease in REE exceeded that for measures of lung function, suggesting that the explanation for the decrease does not relate only to a possible decrease in the work of breathing. Stallings and colleagues have suggested that this increase is statistical rather than actual as REE's were not normalised for fat free mass in these studies so the jury may still be out on this aspect of energy utilisation in CF.[233]

Chronic inflammation is a cardinal feature of lung disease in CF. It is thought to precede airway infection. The degree of the inflammatory response increases markedly once chronic infection with *P aeruginosa* develops. How inflammation increases metabolic demands is not understood. Exploration of cytokine activity, hugely elevated in the CF lung, has not shown direct correlations with REE.[234]

Increased work of breathing

With airway obstruction being a cardinal feature of CF lung disease, increased biomechanical work of breathing is inevitable. However its contribution to REE is unclear. That it significantly contributes to difficulty maintaining weight when there is severe pulmonary disease seems clear from studies in diseases such as emphysema,[235] but its contribution to REE in milder disease is probably not significant. As indicated in the discussion of inflammation above, acute changes in lung function do not make a large contribution to changes in REE. Indeed, Naon and colleagues present evidence that the pulmonary function improvement on antibiotics largely relates to improved matching of ventilation with perfusion.[232]

Possible increased REE

Studies in the late 1980s suggested that CF cells had a supranormal energy requirement. With the identification of CFTR, a theoretical base for this possibility appeared since ATP use is central to CFTR activity. However such a 'hypermetabolism' is now thought not to exist as it has not been consistently shown *in vitro* or *in vivo*.[229 236]

Repeated infections

Although probably mediated through inflammatory demands including pyrogenesis, repeated infections deserve mention as a factor inducing increased REE. Pulmonary infections occur frequently in most children and adolescents with CF. The negative consequences of these for energy balance must be understood so that prevention and early treatment of such exacerbations are prioritised in CF management.

Complications of CF

Certain of the common complications are likely to tip the energy balance further in the extra expenditure direction. Liver disease may lead to further fat malabsorption

as a result of decreased bile acid secretion. Excess carbohydrate losses may occur with CF-related diabetes mellitus.

Energy intake in the child with CF (Figure 6.2):

Gastrointestinal problems (anorexia, vomiting, abdominal pain)

A number of mechanisms may lead to reduced intake as a result of gastrointestinal problems. Inadequate control of steatorrhoea is associated with recurrent abdominal pain often aggravated by eating. Reduction in intake of food is often the result. Full blown distal intestinal obstruction syndrome affects many children with CF. This results in repeated episodes of poor intake.

Gastro-oesophageal reflux is common in CF. If this is complicated by oesophagitis, anorexia is a likely accompaniment.

Respiratory infections

While a decrease in intake during respiratory exacerbations associated with CF would seem likely, this has not been proven scientifically. Reilly and colleagues examined 14 CF patients during treatment for a pulmonary exacerbation using a food intake diary and found a mean reduction of 47kJ per kg of body weight per day.[237] However McCloskey and colleagues using similar dietary methodology were unable to show a difference in intake between patients when well or during a pulmonary exacerbation.[238] Similarly Stallings and colleagues showed no decrease in intake but the population they studied were taking in nearly twice the recommended energy for CF![233] All three found little change in energy balance.

Eating patterns

There is good evidence for altered eating patterns in CF. These are sufficient to threaten adequate nutrient intakes. The most comprehensive studies have been undertaken in the USA by a group led by Lori Stark. Both toddlers and school age children have longer meal times than controls, parents use more coaxing techniques and are more concerned about their children's eating patterns.[239-40] While energy

intakes differed little from controls they mostly did not reach those recommended for CF patients.

International trends in growth of children with cystic fibrosis in the 1980s and 1990s

The ground work for study of nutritional status and growth in CF was set by Shwachman in the 1950s. The inclusion of growth and nutrition in his scoring system emphasised its role in clinical well being in CF.[10] Corey and colleagues' study comparing growth and nutritional status of CF patients in Toronto and Boston brought the critical prognostic role of nutrition to international attention.[16] This study examined patients up to 1982 and therefore can be said to reflect the effects of care in the 1970s and before. After the age of 8 years, the mean height of Toronto patients approximated the normal curves, while those of Boston were significantly below (42nd percentile for males, 33rd percentile for females). Weight percentiles for both populations were significantly below the age norms from early childhood; again Boston patients fared worse than those in Toronto. This study precipitated further attempts to maximise nutrition and growth in CF patients. Many centres and countries published their data in the following two decades.

In the USA, the CFF Registry has led to a number of papers on nutrition and growth. Reflecting CF care in the 1980s, FitzSimmons charted the 'changing epidemiology of cystic fibrosis' in 1993.[140] Her cross-sectional data from 1990 showed that 50% of patients were below the 10th percentile for height or weight. About 15% were above the 50th percentile for these parameters. The most comprehensive study from the Registry examined the nutritional status of 13 116 patients in 1993 from a number of anthropometric angles.[241] Percentile charts were constructed using height and weight for age; these were compared with NCHS percentiles. Beyond the very earliest ages these percentiles deviated greatly from the norm. By teenage the 50th percentile for male height for CF patients approximated the 5th percentile for normal subjects. The effect was much the same for weight but with a much larger downward deviation of the CF 5th percentile. The curves for females deviated even further for weight than those for males but the height percentiles, though lower than for normal subjects, did not deviate as much. The same effect was seen when *z*-scores were used.

The CF working group in the UK has also published percentile charts covering aggregated data for CF centres in the whole country.[242] These measurements were performed in 1994/5 on 3 056 subjects. *Z*-scores for height and weight, and body mass index (BMI) were all below 1990 UK norms for persons less than 23 years of age with height being the best preserved index. The authors noted that there had been an improvement of 0,5 in this standard deviation score compared to USA data from 1975. When their measurements were presented as percentiles, British children approximated population norms for growth indices for longer than their counterparts in the USA (in most cases to 10 years of age). By adulthood the percentile deviation reflected the pattern seen in the USA. It should be noted that USA data included patients not attending specialised CF centres; the UK data did not.

A Danish study of 223 subjects reflected growth in patients attending the Copenhagen CF Clinic over many years.[243] In 1989, height was normal though adult height was achieved later than the norm. Weights were normal for males below 15 years of age and females below 10 years of age. Ten percent of male and females were below the 10th percentile for height and 9% for weight. BMI also approximated the norm in younger patients but deviated significantly after 20 years of age. These data represent the best growth so far shown in a population of CF patients.

In an attempt to chart change within these two decades workers in Queensland, Australia, compared the growth of children under 18 years of age in 1986 and 1996[244] (rather as we did – see below Study 6.2). In their cross-sectional study they found *worse* growth in the latter year, especially among boys! However the patients in 1996 were older on average than in those in 1986 and may therefore have been sicker (indeed their lung function was worse). It was a pity that stratifying by age group was not carried out (as we did) as trends in the growth in younger children may have given a more detailed view of growth trends over time.

One of the putative motivations for neonatal screening in CF has been that early intervention will prevent the growth deficits seen in early years and may prevent later growth deficits, too. Data such as that presented by the UK growth study[242] (in which screening was not the norm) shows rapid 'catch up' growth after the diagnosis of CF but normal growth is not necessarily achieved. Screening aims to bypass this potentially deleterious phase of CF.

Newborn screening has been undertaken in Australia since the early 1980s. In their assessment of 15 years of experience Waters and colleagues in New South Wales compared children identified in the four earliest years of screening with those born in the four years preceding the introduction of the programme.[245] They were at pains to point out that the two groups were likely to have received the same care but this cannot be known with certainty. As predicted the screened group had a greater proportion of children who had PS, but allowing for this, screened children still grew better than non-screened children. Height and weight standard deviation scores were greater at diagnosis and longitudinally to age 10 years. At 10 years screened children were an average of 2,7cm taller than the non-screened historical controls. Notably measures of lung function were also better in the screened group.

The Wisconsin randomised controlled study of neonatal screening in the USA has now demonstrated that better growth is achievable through screening.[150] At diagnosis screened infants were significantly longer and heavier than the control children. For example, the median weight *z*-score of the screened group was –0,5 while that for the control groups was half a standard deviation lower at –1,0. The screened children also had better head circumferences; a demonstration of how significant nutritional deficits have been in early life with CF. Height *z*-scores were consistently lower in the control group right through to the age of 13 years (the maximum follow up time). The screened group had a normal height for age *z*-score through childhood, a demonstration that height deficits are not intrinsic to CF. Notably energy intake in the two groups was the same suggesting that early deficits in growth due to CF have long term effects on stature and head circumference.

A review of screening programmes (only available to me in abstract form) summarises these as follows:

> The literature consistently shows evidence of benefits and lack of harm from newborn screening for CF.[246]

Improved growth outcomes have now been demonstrated in centres of excellence for CF care. The Danish study cited above is one example.[243] The same was noted in Cambridge, UK.[247] In Newcastle in New South Wales, nutritional expertise offered to children from birth in a CF centre has been shown, even in a short period (1993 to 1997) to improve growth in a CF population.[248] The cohort who had had specialised centre care had normal *z*-scores for height up to the age of 15 years; those in the earlier cohort who had fewer years of such care deviated from the norm by 10 years of age. This was in a largely screened population, showing that screening alone is not a guarantee of improved growth.

It should be noted that, despite the achievement of normal growth in early childhood and adolescence in CF in many parts of the world, an Australian analysis of total body potassium levels, a proxy for body cell mass, showed significant deficits in children whose growth indices are normal.[249] In their population only 7,5% of subjects were malnourished according to weight and height *z*-scores yet 29,9% of males and 22% of females had total body potassium levels of less than the cut off level for abnormality of 80% expected indicating much greater levels of actual under-nutrition.

In summary, improvements in the growth of CF populations have occurred through recent decades. Deficits still occur in many patients with the proportion rising to high levels among older patients. Approximations to genetic potential for growth are more likely in the presence of neonatal screening and access to a specialised CF centre.

Literature review of South African experience of nutrition and growth in cystic fibrosis

There is very limited South African literature on this subject. In his thesis on CF, Super gives a number of case reports but nutritional details are sketchy.[31] A picture of slow growth and delayed puberty emerges in those patients who survived infancy. Parenteral treatment with Intralipid, fashionable at the time,[216] was tried on a few occasions. High protein, low fat diets were the norm.

In their report on 33 adolescents and adults with CF (94% of whom had had the diagnosis of CF made during childhood) in Johannesburg, Lewis and colleagues noted that 70% of the patients had 'normal height'.[32] Ninety percent of patients were below normal weight for height (WFH). The authors suggested that this related to the severity of their lung disease (92,5% were hypoxaemic in room air) rather than to pancreatic insufficiency (PI). No description of nutritional management protocols at the adult CF clinic was given.

Up to the time the studies reported in detail in this chapter were published, the only report on the clinical status of South African children with CF also came from the Red Cross Children's Hospital. Hill and colleagues' report includes nutritional parameters in a comprehensive description of CF in Cape Town in the mid 1980s.[33] The nutritional status of the 64 patients alive at that time is given. Thirty six percent were under the 3rd percentile for weight and 24% for height indicating a significant prevalence of malnutrition. The report does not give further details except to suggest that coloured patients were more malnourished than their white counterparts.

"Strenuous efforts to improve their nutrition...."

are recommended in the Discussion, showing appreciation of the importance of good nutrition in CF.

Simultaneous with the gathering of data for this study, Henley conducted a detailed study of patients', parents' and siblings' understanding of CF and their information needs. With respect to understanding of the nutritional aspects of CF, she reported that the

> ..main constituents of familiar foodstuffs were well-known but practical application of this knowledge was often poor.[38]

Of great significance for potentially restricting growth was the fact that 90% of patients believed that fats should be totally excluded from the diet. Parents' understanding was not much better at 50%. In mitigation was a 44% need expressed by patients for 'a great deal more information' on 'what kinds of food to eat to increase your weight'. A quarter of mothers claimed not to have received any nutritional advice and two in three wished for 'a great deal more information' on healthy meals for their CF-affected child.

The fairly dismal figures for growth presented in Hill and colleagues' report were a spur to Study 6.1 which will now be reported. What was the situation in the 1990s and were the children taking in sufficient energy to sustain good growth? Should the emphasis be on enzymes or energy?

This study undertaken with Ms Romy Saitowitz, a newly graduated B.Sc Hons (Dietetics) from UCT whose Honours thesis had reported on the calcium status of the children with CF at the RCCH CF Clinic,[184] was published in the *South African Medical Journal* in 1999 and is reproduced here as it appeared then.[55] **References are given at the end of the report.**

STUDY 6.1

GROWTH AND NUTRITION IN SOUTH AFRICAN CHILDREN WITH CYSTIC FIBROSIS

ATR Westwood

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Cystic fibrosis (CF) is the most common life threatening genetic disease amongst Caucasoid groups. It is characterised by chronic lung disease and nutrient malabsorption both of which significantly compromise growth.[1] The life span of individuals with CF improves with nutritional status[2] probably as a result of a reduction in the rate of progression of the lung disease in better nourished patients.[3] Nutritional management is one of the central tenets of CF care.

In the past 4 decades major strides have been made in the nutritional management of CF. It has been recognised that high dietary energy intakes may be required to achieve optimal growth and nutrition. An average energy intake exceeding 120% of the recommended daily intake (RDI) of non-CF patients is advised.[4] Fat should constitute 35% of dietary energy intake.[4] The development of efficient and effective pancreatic enzyme replacement formulations has made it possible to minimise malabsorption. Coinciding with better survival rates amongst CF patients are recent reports from Western countries that indicate that, in the first decade of life at least, normal growth indices can be achieved in almost all young CF patients.[5 6]

Survival of CF patients in South Africa lags a decade behind Western countries.[7] In a clinical and epidemiological study of CF conducted at the Red Cross War Memorial Children's Hospital, Cape Town in 1986, 36% of patients were below the 3rd percentile for weight and 24% below this level for height.[8] Henley and Hill's report at around the same time showed that there was widespread ignorance of the nutritional principles of CF care amongst families dealing with the disease.[9] If the survival of CF patients in South Africa is to improve, careful attention will need to be given to their nutritional care.

The present study was undertaken to provide up-to-date and detailed data on nutritional status and its dietary correlates in our CF Clinic population. Such data will equip CF management teams to intervene more effectively at the individual and clinic levels to improve the nutritional status and thus the prognosis of CF patients in South Africa.

METHODS

The study population consisted of children and adolescents who received regular care from the CF Clinic at the Red Cross War Memorial Children's Hospital in Cape Town. This Clinic is attended by almost all children and adolescents with CF in the Western Cape. Patients under 2 years, those on continuous home oxygen therapy and, for logistical reasons, those living more than 60km from Cape Town were excluded.

Weight was measured using a scale accurate to 0,1kg. Height was measured with a stadiometer (Seca, Germany) accurate to 0,5cm. Mid-arm circumference (MAC) and triceps skin fold thickness (TST) were measured using a plastic tape measure and a Harpenden calliper respectively. The weight and height measurements were transformed to percentage of ideal weight for age (WFA), height for age (HFA) and weight for height (WFH) using National Center for Health Statistics percentile charts.[10] WFH of less than 90% of expected was taken to indicate malnutrition.[4] Percentiles for the upper arm indices were obtained from Frisancho.[11]

Each family was supplied with an electronic scale to weigh all the food and drink the patient consumed over 3 consecutive days (2 week days and 1 weekend day). From this

3-day weighed food record each patient's daily dietary intake of energy, protein, fat and carbohydrate was calculated using the Foodfinder computer program (Version 1.10, National Research Programme for Nutritional Intervention, 1992). Stool was collected over the same 3 day period for stool fat estimation.[12] A coefficient of fat absorption less than 93% defined steatorrhoea.[4]

Statistical analysis was undertaken using the Statistica computer package (Version 5.1 Tulsa, USA 1997).

RESULTS

Of the 45 eligible patients, 38 (ages 2-18 years, median 10 years) completed the 3 day weighed food record. The Table shows their anthropometric indices. TST and MAC measurements were taken on 21 of the 38 patients. Classification of nutritional status is in accordance with the recommendations of the Consensus Committee of the CF Foundation.[4] One patient did not have pancreatic insufficiency. Median WFH was 93% (interquartile range 84-101%). Forty seven percent (8/17) of patients 10 years and older had WFH below 90% expected. In contrast, 14,3% (3/21) of those under 10 years of age had WFH below 90% expected. The difference was significant (χ^2 = 4,33, p = 0,037). Mean HFA was 96% (SD 4,7%).

Table 1: Anthropometric indices in CF patients

	Frequency (%)
WFH >110% (overweight)	5,4
WFH 90-110% (normal)	62,2
WFH 85-89% (underweight)	5,4
WFH 80-84% (mild malnutrition)	13,5
WFH 75-79% (moderate malnutrition)	5,4
WFH <75% (severe malnutrition)	8,1
HFA <5th percentile	16,2
MAC <5th percentile*	38,1
TST <5th percentile*	28,6

*N = 21

Daily energy intake exceeded 120% of the RDI in 8,1% of cases while 68,6% of patients consumed less than 100% of the RDI. There was no correlation between WFH and daily energy intake (r = 0,034, p = 0,84). Fat intake represented 29,6% (interquartile range 27,5-33%) of daily energy intake. Protein and carbohydrate constituted a median of 16% (interquartile range 13,9-18,2%) and 51,7% (interquartile range 49,9-56,8%) of daily energy intake respectively.

Nineteen pancreatic insufficient patients (51,4%) completed the 3 day stool collection. The median coefficient of fat absorption was 89,09% (interquartile range 81,7-96%) with 7 patients (36,8%) achieving absorption coefficients above 93%.

DISCUSSION

Nutritional management is a cornerstone of CF care. The Consensus Committee of the CF Foundation advises regular monitoring of growth and energy intake as well as regular expert dietary guidance for CF patients.[4] WFH is the recommended growth index for the assessment of nutrition in CF.[4]

One third of patients 18 years or younger in this study had low WFH. That this deficit was nutritional in origin is supported by the similar proportion of patients with upper arm

indices below the 5th percentile. In 16% of patients malnutrition had led to stunting of growth although the mean height of 96% of expected was almost that of the normal population. The majority of malnutrition was found in patients 10 years of age and older. Only 3 of the 20 patients aged between 2 and 10 years (all of whom came from poor social circumstances) had WFH less than 90% (81%, 89%, 73%). It is important to note that infants and patients with very severe lung disease in whom nutritional deficits are common were absent from this analysis.

The nutritional status in CF patients reported here is surprisingly similar to reports from better resourced centres. Using Body Mass Index (BMI) as a measure of nutritional status, the most recent report from the UK CF Survey[5] shows that, after the first two years of life, mean BMI remains in the normal range until the age of 10 years and then declines. Likewise North American 5 to 10 year olds with CF have WFHs in the normal range.[6] Reports from other centres published in the 1990s show a similar proportion of stunted patients to our cohort (Morison et al.: 14%[13], Wootton et al.: 17%[14]). However, in common with comparable studies[5,6], we have shown that, for the majority of young patients with CF, stature in the normal range can be expected.

In our study, nutritional status after the first decade of life deteriorated to the point where 47% of patients were malnourished. In contrast, similar patients in the UK have a BMI less than one standard deviation below population norms[5]. Declining adherence to therapeutic and dietary regimes amongst adolescents is common. Compared with the UK, South African CF Clinics have fewer clinic and community resources to counteract this tendency. Given the poorer prognosis of CF in South Africa[7], adolescents are likely to have more severe lung disease than their UK counterparts. This will also make it more difficult to achieve adequate nutrition and growth.

Intuitively it would seem probable that those with the lowest relative energy intake would have the greatest degree of malnutrition. We were unable to show this. This may reflect the small sample although two studies with similar numbers of patients were able to show some correlation between energy intake and measures of nutritional status.[13,14] This lack

of correlation may also throw doubt on the accuracy of the weighed food records. However other results based on these records were in accord with previous studies in CF patients. For example, the finding that most patients did not reach the normal RDI for energy or fat, let alone the higher intakes recommended in CF, is not unique to Cape Town.[14 15]

Despite the relatively low dietary energy and fat intakes, 67,6% of our patients had achieved WFH above 90%. This apparent paradox may be because CF patients, on average, weigh less than their peers.[13] As Wootton et al[14] point out, since RDI is calculated on an individual's age rather than weight, energy needs in CF will be overestimated.

Our results indicate that dietetic advice needs to be individualised, with specific attention being targeted at those with declining WFA, HFA or WFH and those approaching their teenage years. The emphasis will need to be on increasing fat intake as patients with higher fat intakes absorb higher amounts of energy.[13]

Only half the patients completed the 3 day stool collection. Despite pancreatic enzyme replacement therapy and in common with their counterparts in developed countries,[6 13 14] the majority of patients tested were malabsorbing fat. This will have contributed to energy deficits and consequent malnutrition. Further education and closer attention to the detail of enzyme use will be necessary to improve fat absorption.

The gains made in the prognosis of CF in recent decades have largely been due to the greater attention given to the details of conventional care i.e. dietary management, pancreatic enzyme replacement therapy, physiotherapy and treatment of respiratory infections. Our study has shown that, with respect to nutrition, the majority of our young CF patients compare well with patients from better resourced countries. However, it is also plain that for some patients and especially for adolescents[1] greater attention to nutritional care and enzyme use is needed both of which require ongoing expert medical and dietetic care. The data in this study were collected in part to assist in tailoring advice

to the individual and family. The recognition of persisting dietary energy and fat deficits and the need to maintain gains made in the first decade of life has led to the publication of a South African book of nutritional advice for families dealing with CF.[16]

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At the same time as this study was being undertaken and analysed I had been examining the prognosis of CF in the Cape Town population since 1974. I was unable to show an improvement in the outlook of the disease despite the clinical impression of such progress (see Chapter 9 for the full study).[52] I decided to explore what had happened to the nutritional status of patients attending the clinic over time. Any improvement demonstrated might stand to bolster a sense that we were on the right path in our management of the disease. The idea was a simple cross-sectional comparison of anthropometric measures over time. The paper arising from this study appeared in the *Journal of Tropical Pediatrics* (whose editor did not hold Cape Town's latitude against information of the health of its paediatric population).[56] Once more the references appear at the end of the article.

STUDY 6.2

CHILDREN WITH CYSTIC FIBROSIS IN SOUTH AFRICA: AN IMPROVING NUTRITIONAL PICTURE.

Westwood ATR, Ireland JD.

J Trop Pediatr 2000; 46:119-121

SUMMARY

Nutritional status and growth play an important part in determining prognosis in cystic fibrosis (CF). In South Africa, the median survival of patients with CF is 18 years. Using chart review, we studied the pattern of growth over time of a South African CF population. Percentage of expected weight for age, height for age and weight for height were determined for each patient in 1986 (N = 49) and 1996 (N = 63). Mean indices were the same in the two years. In 1996, mean weight for age of children aged 5-10 years was 94,2% (SD 20,4), 14,3% higher (p = <0,05, 95% confidence intervals 3-25%) than children of the same age in 1986. Improved growth of young children with CF has been achieved in a resource poor country setting the scene for improved prognosis.

Cystic fibrosis (CF) is associated with progressive obstructive pulmonary disease. The majority of persons with CF also have pancreatic insufficiency. These two conditions together with decreased appetite, recurrent chest infections and a high resting energy expenditure make it difficult for persons with CF to maintain adequate growth.[1]

Since the identification of the disease in 1938, its prognosis has steadily improved in most countries[2] with the enhanced growth of persons with CF being an important contributory factor.[3] In South Africa, cystic fibrosis occurs in 1 in 2000 births amongst Caucasoids and 1 in 12000 births amongst persons of mixed ancestry. A recent study of the prognosis of CF in the Western Cape region of South Africa showed median survival to be about 18 years.[4] This study was not able to demonstrate a difference in survival

between persons with CF born in the decades 1975-1984 and 1985-1994. This was probably due to a preponderance of infant deaths (some infants were mistakenly thought to have kwashiorkor[5]) and the size of the cohort. To establish whether progress has been made in setting the scene for improved survival in this region, we compared the growth of patients with CF in 1986 and 1996.

PATIENTS AND METHODS

The charts of all patients with CF regularly attending the CF Clinic at the Red Cross War Memorial Children's Hospital, Cape Town in the first 6 months of 1986 (Group 1) and 1996 (Group 2) were reviewed. Patients diagnosed less than a year prior to these periods were excluded as their weights might not have stabilised following the institution of therapy. Each patient's maximum weight (kg) in the 6 month period, the associated height (cm) and age (years and months) were recorded. These were converted to percentage of ideal weight for age (WFA), height for age (HFA) and weight for height (WFH) using National Center for Health Statistics growth charts.[6] The groups were compared *in toto*, by sex, by ethnic group and in 5-year age groups.

RESULTS

Group 1 had 49 patients (24 male) and Group 2 had 63 (35 male). WFA, HFA and WFH data are shown in Table I. There was no difference in mean WFA. Insufficient height measurements were available for 1986 for comparisons of HFA and WFH to be made.

There were no significant differences between the two groups when compared by sex and ethnic group (data not shown).

Table I

Nutritional Indices: 1986 vs 1996

	WFA		HFA		WFH	
	Number	%(SD)	Number	%(SD)	Number	%(SD)
Group 1 (1986)	53	83,4(14,6)	12	95,7(4,6)	12	89,1(15,7)
Group 2 (1996)	63	83,6(22)	60	95(5,5)	60	87,9(20,5)

SD = Standard deviation

Table II

Weight-for-age by 5-year age group

	< 5 years		5-10 years		10-15 years		> 15 years	
	Number	%(SD)	Number	%(SD)	Number	%(SD)	Number	%(SD)
Group 1 (1986)	16	93,1(14,1)	20	79,9(13,2)*	10	74,9(13,5)	7	83,2(12,9)
Group 2 (1996)	14	91,4(9,1)	18	94,2(20,4)*	21	79,1(25,9)	10	62,9(11,6)

*Difference = 14,3% (p = <0,05 95%CI 3-25%)

Table II, showing the groups analysed in 5-year age groups, demonstrates a significant improvement in WFA for those aged 5-10 years.

DISCUSSION

While WFH is a better measure of the nutritional contribution to growth in CF, low WFA does reflect the effects of the disease on growth.[7] There was a significant improvement in the growth of patients with CF in the Western Cape in the decade under review. The 14,3% improvement in mean WFA for 5-10 year old children translates into a shift from the 10th percentile to just below the 50th or an increase in Z score of 0,5. Thus, in 1996, CF was having a minor influence on the growth of most children in this age group.

For the 10-15 year old patients, the number of whom have doubled between 1986 and 1996, the large standard deviation in 1996 suggests that a subpopulation of patients is doing particularly badly while most may be better off than their peers of a decade before. The raw data support this: 3 patients in this age group had WFA below 55% in 1996

compared with none below 60% in 1986. With a mean WFA of 79,1%, patients aged 10-15 years in 1996 are of equivalent WFA to a group 5 years their junior in 1986. This is further evidence of improved growth in the 1996 group. These improvements in the growth of patients under 15 years of age should result in improved survival.

The apparent decline in the status of patients over 15 years of age is misleading because an adult-oriented clinic was established in 1989 at a separate site. In 1996 only the most debilitated patients over 18 years of age remained at the Children's Hospital Clinic.

What has brought about these improvements? Effective enteric-coated pancreatic enzyme supplementation was available before 1986 although its improved control of steatorrhoea may not have reversed the nutritional effects of prior malabsorption. The recognition of the value of high fat diets in preventing malnutrition in CF became general before the years under scrutiny but had not been fully implemented in 1986. Subsequent interventions which may have contributed to the near normalisation of WFA in young children with CF are greater dietetic involvement, greater use of nutritional supplementation including gastrostomy feeding and the more aggressive use of a greater range of anti-pseudomonal antibiotics. The improved recording of height data in 1996 is testimony to better growth monitoring which is leading to earlier recognition of faltering growth. Appropriate intervention can then take place.

In the mid-1980s a study of patient and parent understanding of CF in Cape Town showed poor insight into the nutritional aspects of care.[8] Whether this has been reversed in the intervening years is unknown. Recently a South African book of nutritional advice for families dealing with CF has been produced.[9] Earlier identification of children with CF is probably not a factor in the improvement in growth as delayed diagnosis remains the norm. Only 3 patients in this study were pancreatic sufficient, a status which usually results in better nutrition.

These positive trends have been achieved despite reductions in services and support for those with uncommon diseases which require specialised health care in South Africa.[10 11]

They give cause for encouragement for South Africans with CF and their carers. Improved growth and nutrition can lead to improved health and thus enhanced quality and length of life. The gains made over the last decade will need to be maintained by careful attention to all aspects of CF care. Services geared to achieving this need to be sustained.

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CRITIQUE & COMMENTARY ON CAPE TOWN STUDIES

These two cross-sectional studies added significantly to the South African literature on nutrition in CF. They demonstrated that many children were growing well. The studies were not designed to test whether those children were growing optimally but they presented an encouraging view given the challenging circumstances in which health care was being delivered. That progress was being made over time (albeit only measured by weight for age (WFA)) was also encouraging, given the importance of good nutrition in improving the prognosis of CF. The studies demonstrated the danger adolescents were in from a nutritional standpoint. Although our discussion expressed the view that this might reflect the effect of poor lung function, it equally could have been that the poor nutrition was setting the scene for rapidly progressive lung disease. The care of adolescents became a focus of our CF care in part as a result of this study (see Chapter 8).

Although there was a considerable amount of useful, information contained in these two studies, there were significant gaps. Infants and those with advanced lung disease were missing. Rural patients had not been assessed in detail. There was no longitudinal information. In only 38 patients had height been studied so the 16,2% prevalence of HFA less than the 5th percentile must be regarded as preliminary. The majority of patients (67,6%) had good WFHs, but were these masking less than adequate linear growth, a marker of poor early nutrition? The effect of gender, ethnicity or socio-economic status were not covered. Given the deleterious effect of female gender on CF[136] and the fact that coloured patients have a worse outlook than white patients,[52] such detail might be illuminating in our context. There has also been no correlation of nutrition with lung function. Ms Saitowitz and I analysed nutrient intake beyond the macronutrients described in Study 6.1 using the 3 day food record but a wide scatter of results with no correlation to anthropometric or macronutrient intake made interpretation impossible. Further targeted studies such as Saitowitz' calcium studies[184] might be a better approach.

As discussed in the introduction to this chapter, good nutrition has established itself as central to the quest for better survival outcomes in CF. From Hill and colleagues' study[33] that outlined overall nutritional status through Henley's thesis exploring nutritional knowledge among patient and family members[38-9] to our studies, there has been a progressive desire for nutrition to take this central role in Cape Town. The sub-optimal energy and fat intake of a considerable proportion of the children studied acted as a spur to improved dietetic management at the Clinic. Since the mid 1990s a dietician has attended all clinics and measured height and weight and calculated WFH at each patient visit, as recommended by the CFF Consensus Committee in 1992.[228] This information has then been available to the medical staff at the time of their consultation with patient and parent. The clinical record was designed to make reference to previous anthropometry easy (see Appendix B). A graphical representation of WFH was available on the inside cover of the CF folder, the aim being to allow early recognition of growth faltering. Growth faltering has been the signal for further anthropometry such as upper arm measurements as well as more detailed dietetic assessment. Nutritional supplementation in the form of proprietary nutritional products has been available under the guidance of the CF Clinic's dietician. Gastrostomy feeding using the PEG method was introduced for patients who failed to grow despite maximal optimisation of PERT and full dietetic intervention including caloric supplementation. Fourteen patients have had supplemental feeding by this route between 1994 and 2002. (Further details are given in Chapter 5 (p155). Regular faecal fat measurement as recommended by Littlewood[181] and others was not introduced as, even under study conditions, few families completed this unpleasant study. A project to produce a nutritional advice booklet for South Africans with CF was funded with an award from Solvay Pharmaceuticals in 1995. A 100 page book entitled 'Eating, Enzymes and Exercise'[250] that contained advice about all aspects of nutrition in CF (compiled and written by this author) and dozens of recipes (devised by Ms Saitowitz and CF patients and their parents) was published and distributed in 1997 with a revised second edition appearing in 2003.

The deficiencies in our studies and the changes wrought in the management of patients over recent years should encourage further evaluation of the nutritional status of patients in this region (and in the whole country).

Internationally, a number of changes in the approach to nutritional evaluation and management have taken place that could influence how this evaluation might be done.

Proportional hazards statistical techniques have been applied to longitudinal data in CF, even in relatively small CF populations. For example, Oliviera and colleagues, in a Brazilian CF population of 127 subjects, were able to show that HFA at diagnosis could influence prognosis.[251] A HFA *z*-score of more than –1,29 was associated with the 97% (95% CI 93-100) estimated survival; less than –1,29 and the survival estimate dropped to 66% (95% CI 52-80). This effect remained on multivariate analysis: relative risk 4,06 95% CI 0,92-17,8).

Further thought has been given to which nutritional measurements give the best assessment of growth in CF. A 1998 paper published by a group studying the CFF Registry sought to compare a range of anthropometric indices in CF.[241] These included comparisons with normal percentiles (HFA, WFA etc.), percent expected WFA and WFH medians, *z*-scores, and measures of adiposity such as BMI and percent ideal HFA. Using four criteria for malnutrition based on the literature, they demonstrated that these measures produce different and sometimes conflicting assessments of malnutrition in CF. For example, while the proportion below the 5th percentile and those with a percent of median WFA <80% and HFA <90% identified a similar proportion to be malnourished, they did not agree on whether the children were stunted, wasted or both. Of note, the criterion that identified the least number of children to be wasted and stunted (3,9% compared with 11-17% by other criteria) included measures recommended in the 1992 Consensus statement[228] (HFA <5th percentile, percent ideal WFH <85%). The researchers noted that, in practical terms, HFA and WFA percentiles are the easiest to compute. The meaning of more detailed definition of 'malnutrition' in terms of wasting and stunting has yet to validated in CF, they felt: '...longitudinal growth data is

necessary to address these questions.' Anthony and colleagues in Melbourne, Australia cast further doubt on the value of percent ideal WFH as a measure of growth in CF in their study of CF subjects and their siblings.[252] CF subjects were distinguishable from their siblings by height and weight *z*-scores and BMI (their scores were significantly lower) but not by percent ideal WFH.

Since our studies were conceived and published, the 1992 Consensus document on nutrition in CF has been superceded by another, published in the *Journal of Pediatric Gastroenterology and Nutrition* in 2002.[253] This document related growth measures to the new NCHS/CDC charts of 2000[254] (see next paragraph for a discussion of these charts in relation to SA). HFA and percent ideal WFH remain the recommended routine assessments of growth. The latter, updated with recent methodology, remains a calculated parameter. BMI percentile has been added as the NCHS/CDC charts include this measure. In assessing whether a patient is nutritionally compromised, height is related to predicted height (on the basis of parental heights). Percent ideal WFH should be ≥90% expected with no weight loss or plateau for 'acceptable' nutrition to be pronounced by the CF team. It is surprising that WFH is retained in the assessment of nutritional status on CF given the doubts cast on its usefulness by some the Consensus Statement's own authors! McNaughton and colleagues in their study of total body potassium levels in CF also showed WFH to be the least sensitive measure of true nutritional status.[249]

The two Cape Town studies reported in this chapter used the older NCHS percentile charts that have been accepted in SA. In 2000, the CDC in the USA published new growth charts. These charts, also cross sectional and based on an American population, aimed to correct some of the demographic imbalances of the 1977 charts.[254] They also aimed to smooth out the 'disjunction' between length and height charts. For the first time BMI charts were given. Overall, ranges of normal were somewhat extended as a result of the new anthropometric data. Whether the NCHS/CDC charts of 2000 would alter nutritional classification of South African children has not yet been tested. Our studies reflect the growth of children with CF relative to norms that have been applied (as the

best available) to South African children. Study 6.2, with its comparative cross-sectional design, compared groups across time using identical growth norms. Should future studies of the effectiveness of the strategies to improve nutritional and growth in CF patients in the Western Cape province outlined above continue to use NCHS percentiles for retrospective comparisons to be valid, or should we be comparing our CF patients with those in other centres that now base their norms of the NCHS/CDC charts (USA) or MRC charts (UK)? Given the socio-economic determinants of growth in childhood in SA, I believe that we should continue to compare our CF children with current South African norms and previous generations of CF children in SA i.e. use the 1977 NCHS charts with all their imperfections. In view of the significant levels of nutritional compromise demonstrated in our CF population, the caveats surrounding WFH are less pressing in SA. WFH estimations, especially when followed over time, are likely to add value to clinical anthropometry in our context. It would be interesting to see how our children fare on the new BMI chart.

There is good evidence that nutritional interventions such as those we have used in Cape Town work. A meta-analysis of nutritional interventions published in 1997 showed behavioural interventions to be most effective in producing weight gain in patients with CF. Oral, enteral and parenteral supplementation were also found to be effective when studies were combined.[255] It would be important to monitor their effect in our context.

Future studies of nutrition and growth in cystic fibrosis in South Africa: Recommendations

As argued above there are good reasons to continue to monitor and study the nutrition and growth of patients with CF in SA. In addition, existing data from the time from when height has routinely been measured in Cape Town should be mined for further analysis (e.g. gender, ethnic group, the larger number of adolescents who have been seen since 1996). The following practical approach is recommended in the light of experience and study:

Measures

1. Continue routine, accurate measuring and recording of weight and height in specialised centres.
2. Percent ideal WFH should be calculated as recommended by the CFF Consensus report.
3. BMI percentile to 20 years of age.
4. Head circumference through infancy.

These measures should be part of the national CF database that is in evolution.

Analysis

1. Based on NCHS percentiles (except for BMI)
2. Cross sectional comparisons over time (age groups or specific ages)
3. Longitudinal charting of individual children in age cohorts
4. Gender-matched comparisons for cross-sectional and longitudinal data
5. In Cape Town, ethnic differences in prognosis mandate comparisons between coloured and white children.

These measures and analyses will allow audit of expensive services, optimisation of interventions and use of the data in studies of other aspects of CF in SA such as prognosis and lung disease.

CHAPTER 7

LUNG DISEASE ASPECTS

OUTLINE OF CHAPTER

The present chapter reviews what is known about CF lung function and microbiology in South Africa and reports a new study of the microbiology of CF lung disease in our population. The limitations of longitudinal data on measures of lung disease so far in this population are demonstrated. The chapter then explores how routine data might be used to yield useful information for clinical audit and patient care in South Africa.

INTRODUCTION

A large proportion of the morbidity and nearly all of the mortality associated with CF is related to lung disease. Yet despite this central role the range of patterns of lung disease is very wide. While the pathogenesis follows a uniform sequence (early inflammation, infection with respiratory viruses and typical bacteria, increasing endobronchial disease, progressive destruction of lung parenchyma and airways leading to bronchiectasis and cystic change, the development of respiratory failure), the speed at which this occurs is determined by genetic, environmental and health service factors.[256]

Many of these factors are known but their influence on and interaction in a particular individual are hard to predict. At a CF population level this wide variation and multiplicity of influences on lung disease limits the value of cross-sectional measures of lung disease such as lung volumes and chest X-ray scores. As Corey in Toronto has clearly argued, longitudinal analysis of these parameters, while more helpful in describing the progression of CF lung disease in a population, is also fraught with complexities.[257] This will be especially the case for a small population spread over many

years such as the one under study here. In longitudinal terms the factor that will have most influenced lung disease in the last 30 years will have been advances in medical therapy. These advances are likely to have outweighed genetic influences on lung disease such as ΔF508 status and immunological phenotype. Other environmental changes such as reduced exposure to cigarette smoke or pathogens will also not have been as significant as the influence of new antibiotic regimens and better nutrition. So how is lung disease to be studied in a CF population such as that in the Western Cape province and what is the value of research done so far?

Chapter 4 presented one aspect: the lung complications associated with CF in the CF population of the Western Cape province. Given that lung disease largely determines the mortality from CF, the influence of changes wrought in medical therapy may be measurable in terms of survival in CF over the period under review. This aspect of lung disease was explored in a 1999 paper[52] and is further explored in the chapter on the prognosis of CF in the Western Cape province (Chapter 9). The microbiology of lung disease in CF in our population is reported in an unpublished study (Study 7.1).

Lung disease in cystic fibrosis in South Africa: a literature review.

The literature on CF lung disease in SA is limited to case reports, reviews of whole populations and cross sectional descriptions. Super's cases were all reported as case reports in his thesis with no attempt to group patients.[31] The first overall analysis of lung disease in a South African CF population came from a review of experience at a newly formed adult clinic in Johannesburg.[32] In this review in the early 1980s, summaries from 33 white CF patients ranging in age from 14 to 32 years were given. The article also described typical practice at the time and was not intended as a scientific review. A picture was given of variable degrees of lung disease with a minority (7%) needing recurrent admission. *Pseudomonas aeruginosa* was grown from the sputum of 82,8% of these patients and *Staphylococcus aureus* from 63,7%. Details of lung function were not given. Radiographic changes were reported as consistent with other larger series. No scoring was done.

The second study to report lung disease was Hill and colleagues' paper from Cape Town in 1988.[33] Again this was a review of all patients seen in a service. Sixty four patients were reviewed cross-sectionally. Lung function was not reported but Shwachman scores (that include clinical pulmonary parameters) were. This was a very young population (67% <10 years of age) and *P aeruginosa* colonisation was uncommon (11/64). One year's worth of sputum cultures associated with pulmonary exacerbations was measured. Typically, *S aureus* and *P aeruginosa* infections dominated.

These two studies allow only limited insight into lung disease in CF in SA. From the information given, one can broadly say that CF lung disease in children, adolescents and adults had the typical features described for CF in other parts of the world.

Zar and the team at the RCCH undertook the most detailed study yet of lung function in CF in the mid-1990s.[258] Perhaps reflecting its origins in the field of gastroenterology, the RCCH CF Service did not measure lung function routinely in CF patients until the beginning of the 1990s. The forced expiratory manoeuvre has been used as a clinical tool in patients attending the outpatient clinic. The most recent data from this clinically based procedure formed the basis for the study which was published, with an editorial updating readers on CF and its local relevance,[259] in the *South African Medical Journal* in 1998.[258]

This study aimed to report details of the pattern and reversibility of lung function and related these aspects to demographic variables, CFTR genotype and infection with *P aeruginosa*. Forty two consecutive children (86% of those eligible, based on age and ability of perform the forced expiratory manoeuvre; ages 5,9 to 18,8 years, mean 11,8 years) were studied when they were well. The main findings of this first view into the lung function of children with CF in SA were of relatively preserved lung function (69% had 'mild' or 'minimal' disease) and worse lung function in the presence of *P aeruginosa* colonisation. Unfortunately the influence of age on this latter finding was not studied: worse lung function and the likelihood of infection with *P aeruginosa* both increase with age in CF. As with the encouraging findings for nutrition reported in Chapter 6, these

lung function data suggested that a springboard for better health in CF existed. Apart from *P aeruginosa* infection, no other factors (gender, genotype) were associated with differing lung function.

As part of my first study on the prognosis of CF in this region, I recorded age at first *P aeruginosa* infection in the 102 patients over a 20 year period.[52] The organism appeared earlier in coloured compared with white patients (median 1 year versus 4 years) and was associated with a lower 5-year survival in this group. This effect was not seen 10 years after colonisation (numbers surviving or followed up for 10 years after infection were small). Full details can be found in Chapter 9.

A number of questions remain after these initial studies of lung disease in our CF patients. What happens to lung function over time? What are the patterns of colonisation/infection with lung pathogens? As the *SAMJ* article[248] asked, are there other variables (e.g. socio-economic status, health care access) that influence lung function in this population? Is the mild lung disease in the earlier years of life leading to an improved survival outlook in CF in this province?

Study 7.1

The Acquisition of Bacterial Pathogens in Cystic Fibrosis in the Western Cape Province

Focused literature review

In the early years after CF was delineated as a separate clinical entity, *S aureus* was responsible for most of the respiratory morbidity associated with the disease.[4] As infection with this organism was controlled with antibiotics, chronic *P aeruginosa* infection became a regular problem and challenge. While the exact relationship between these two infections has been the subject of controversy over the years, recent work studying the infection of children identified as having CF by newborn screening has

suggested that, indeed, *S aureus* infection is a risk factor for the acquisition of *P aeruginosa*. Prospectively studying 180 children born in Denver, Colorado between 1982 and 1989, Maselli and colleagues found that increased numbers of oropharyngeal isolates of *S aureus* were associated with earlier acquisition of *P aeruginosa* (relative risk 1,30).[260] It is also clear from such studies that *S aureus* infection is not a *sine qua non* for *P aeruginosa* infection. Using bronchoalveolar lavage (BAL) to obtain respiratory tract samples in infants, Nixon and colleagues in Melbourne, Australia cultured *P aeruginosa* in a significant proportion of cases (42%) where there had been no prior *S aureus* cultures.[261]

P aeruginosa, an unusual infection in other settings where human subjects are immunocompetent, has a special affinity for the respiratory tract in CF. The organism appears to adhere to CF epithelial cells more easily than to non-CF cells. CFTR may function as a receptor for *P aeruginosa*.[262] It is also possible that local immunological defences such as defensins are unable to protect the lungs against bacterial infection in CF subjects owing to the abnormal composition of the mucociliary layer in the disease. Once established in the lungs, *P aeruginosa* is almost impossible to eradicate; indeed so important is this fact that postponement of chronic infection is vital. This was shown to be possible by Valerius and colleagues in the early 1990s: they showed that vigorous antibiotic therapy could postpone chronic infection in some patients.[21]

P aeruginosa infection is associated with an acceleration of the decline of lung function in CF. It had been suggested that *P aeruginosa* was merely a marker of more advanced lung disease but recent work has put this notion to rest. Rosenfeld and colleagues in a study of very young CF subjects demonstrated that, even very early in life, the presence of *P aeruginosa* is associated with worse lung function even when changes are relatively mild.[263] The Australian study of early acquisition also showed that early *P aeruginosa* infection led to worse outcomes at 7 years of age.[261] The measures identified as worse in children infected with *P aeruginosa* included mortality, FEV_1 variability, National Institutes of Health scores and days in hospital. Likewise the Wisconsin study of new

born screening showed that children's chest X-ray scores and FEV_1/FVC percentages deteriorated accelerated with *P aeruginosa* infection.[264]

P aeruginosa establishes a foothold in the CF lung by changing phenotype and developing a biofilm of exopolysaccharide ('alginate') and microcolonies of organisms. On the culture plate these strains appear as mucoid colonies. Once this change has taken place eradication is much more difficult. The organisms are effectively protected from antibiotics and induce a continuous and self-injurious immunological response in the host. This chronic response by the host to permanent infection sets the scene for progressive lung damage. Henry and colleagues in Australia showed that the mucoid form of *P aeruginosa* was associated with worse survival than its non-mucoid phenotype was.[265] Pedersen and colleagues in Denmark presented evidence that the mucoid phenotype accelerated the deterioration of lung function in CF.[266] This has been confirmed by the latest prospective work associated with the Wisconsin newborn screening study. All measures of lung function (FEV_1, FVC, FEV_1/FVC ratio, FEF_{25-50}) deteriorated more rapidly after the phenotypic change from non-mucoid to mucoid *P aeruginosa*.[267] The recent discovery that macrolide antibiotics such as azithromycin have an anti-inflammatory effect on this biofilm has already been shown to have a positive clinical effect on lung disease in CF,[268] confirming the importance of this alginate layer.

Lee and colleagues have validated a definition for infection with *P aeruginosa* (Table 7.1).[269]

Table 7.1. Stages of *Pseudomonas aeruginosa* infection in cystic fibrosis

Stage	**Proportion of samples growing *Pseudomonas* in last year**
Chronic	>50%
Intermittent	<50%
Free of PA	No growth in previous year
Never infected	Never cultured

PA = *Pseudomonas aeruginosa*

It has become very clear in the last decade from studies using BAL and anti-pseudomonal antibody detection in screened and unscreened newborns with CF that *P aeruginosa* infects the lungs of CF patients much earlier than had previously been thought. Using BAL and oropharyngeal cultures, Nixon in Australia showed that 45% of 53 patients had become infected by a mean of 45 months of age.[261] The methodology of respiratory sampling has been crucial in demonstrating this: when oropharyngeal cultures only are used even in screened children, median age at infection appears to be much later e.g. 8,1 years.[260]

Pseudomonal antibody testing shows the time to infection to be even shorter. Burns and colleagues studied yearly samples of BAL fluid from the airways of unscreened children under the age of 3 years.[270] Seventy two percent had infection either in the oropharynx or BAL fluid; one third had *P aeruginosa* in their BAL fluid in years 2 and 3 of life. All in all, 45% of patients had *P aeruginosa* detected in BAL fluid in the first 3 years of life, a figure very similar to the Australian BAL study. When serology for antibodies to various epitopes of *P aeruginosa* was added to the assessment, fully 97,5% of the 40 patients had evidence of infection. It was also evident that patients may become infected with more than one genotype of *P aeruginosa* and that there is not a unique genotype associated with this early infection. The vast majority of organisms were non-mucoid. West and colleagues in Wisconsin, USA studied CF patients identified through newborn screening. They showed that high antibody titres preceded cultures from the oropharynx by 6 to 12 months as did deterioration in the chest X-ray score. This suggests that the presence of antibodies reflects a clinically significant pulmonary infection. In this study the most

sensitive antibody was that to a whole cell lysate, significant titres being found at a median of 17,8 months of age.[271]

Using BAL, Burns and colleagues' studies[270] confirmed what had already been demonstrated with sputum cultures by Armstrong and colleagues in Australia[272]: the good negative predictive value (NPV) of single oropharyngeal cultures in relation to cultures from the lower respiratory tract (Armstrong and colleagues NPV 96%, 95% CI 91%-99%, Burns and colleagues NPV, 85%; 95% CI, 76%–92%). However they suggested a better predictive value for multiple positive oropharyngeal cultures than Armstrong and colleagues:

> Isolation of P. aeruginosa from the [oropharyngeal] culture was less accurate in predicting lower airway P. aeruginosa isolation ([positive predictive value], 69%; 95% CI,48%–86%). Combining the results of 2 [oropharyngeal] cultures (concurrent with and 3 months before the BAL culture) yielded the highest predictive values of the measures we analyzed (sic). The NPV of this combination of [oropharyngeal] cultures was 97% (95% CI, 86%–100%), and the [positive predictive value] was 83% (95% CI, 52%–98%).[270]

Although Burns and colleagues suggested that, in the light of these findings, two oropharyngeal cultures collected three months apart may be a surrogate for lower respiratory secretions, these CIs are very wide when seen in the light of the decisions required in clinical practice. Thus, until larger studies have been concluded, in circumstances where antibody tests are not available such as SA, lower respiratory secretions should be obtained to confirm clinical infection. BAL is impractical in routine practice; a well-collected sputum sample is the best proxy.

What determines whether an individual child becomes infected with *P aeruginosa*? The study of Maselli and colleagues cited above[260] is the latest in a string of studies investigating this question. They had the advantage of a prospective view of screened

children. The disadvantage of their study is its dependence on oropharyngeal cultures. However since this method was consistent throughout the study and there is no known bias against a single patient group of this method of obtaining respiratory samples, time to positive culture, though falsely long and possibly not reflecting lower respiratory tract infection, is likely to have been proportionately delayed for all subjects. On multivariate analysis female gender was identified to lead to earlier infection during follow up (relative risk 1,85). This confirms the findings of a specific investigation into the role of *P aeruginosa* in the poorer clinical outcomes in CF associated with being female by Demko and colleagues.[273] This study from Cleveland, Ohio showed that females were infected by *P aeruginosa* and became chronically infected by its mucoid phenotype about a year earlier than males. Doubts have been cast on the validity of the study by Maselli and colleagues. Workers from Tuscany in Italy questioned the meaning of 'acquisition' as it merely referred to first culture and not chronic infection by *P aeruginosa*, an important clinical distinction.[274] Their data suggested no difference attributable to sex, though Accurso, one of the authors of the criticised paper wondered if the Italian study had the power to resolve this issue.[275] It should be noted however that in the first study of risk factors a retrospective analysis undertaken using the Toronto patient database, female sex was not found to be a risk factor, but the range of details was less than in the Ohio study. The jury could be said to be out on this question.[276]

As discussed above, in Maselli and colleagues' study,[260] more cultures of *S aureus* raised the risk of *P aeruginosa* colonisation. Zar with colleagues in New York had studied *P aeruginosa* adherence to CF epithelial cells harbouring different CFTR mutations.[262] Homozygosity of ΔF508 led to greater adherence. Maselli and colleagues demonstrated that this may be leading to clinical differences: their homozygous patients had a 123% increased risk for *P aeruginosa* infection.[260] (The table in the paper contains a misprint and attributes this risk to ΔF508 heterozygosity.)

Health service factors may be putting children at risk of *P aeruginosa* infection. Maselli and colleagues identified days in hospital as an association[260] as did Kerem and colleagues in Toronto.[276] Whether it is a risk factor depends on causation, which remains

unclear. A biological risk factor not controlled for in the study may put the children in hospital more often. However three other studies give one pause on this issue. In their demonstration of the benefits of specialised centre care, Mahadeva and colleagues found a greater prevalence of *P aeruginosa* infection in patients attending a specialised centre when compared to a smaller clinic.[247] Likewise the Wisconsin study of newborn screening has shown earlier *P aeruginosa* infection in screened children.[277] It is hypothesised that greater exposure to the health care environment is putting the screened children at risk. The Danes vigorously segregate CF patients according to which lung pathogens they harbour. They claim that, as a result of this practice, *P aeruginosa* infection is delayed, improving survival from CF in Denmark.[278]

Another risk factor for earlier acquisition of *P aeruginosa* appears to be antibiotic use. Continuous anti-staphylococcal antibiotic use in Germany has been shown in a retrospective study by Ratjen and colleagues to be associated with this outcome, particularly under the age of 6 years.[279] A large 7 year prospective trial of cephalexin prophylaxis for *S aureus* by Stutman and colleagues in the USA also showed a greater acquisition of *P aeruginosa* in treated versus untreated individuals (25,6% versus 13,5% p <0,009).[280]

The Wisconsin study of newborn screening suggested that better weight for age seemed to protect against *P aeruginosa* infection.[277] Its beneficial effect on lung disease was only felt if *P aeruginosa* infection was excluded from predictive models.[264] Kerem and colleagues suggested the deleterious effect of poor nutrition to be the mechanism by which their finding of increased risk associated with more gastrointestinal disease (meconium ileus, pancreatic insufficiency) was effected.[276] Other risk factors identified in single studies include inhaled therapy[281] and maternal educational level.[276] Ethnic group has not yet been shown to be an independent risk factor for *P aeruginosa* infection.

There is a number of bacterial organisms whose acquisition in the lung in CF seems to be associated with ecological pressures associated with the vigorous use of antibiotics. The *Burkholderia cepacia* complex is the most studied of these because it has established a

reputation for aggressive and invasive behaviour in CF. In fact this sometimes lethal behaviour is associated with particular genomovars in particular CF contexts. Many other strains exhibit considerably less virulence.[282] *Stenotrophomonas maltophilia* seems to have a virulence profile less than that of *B cepacia* but can cause pulmonary exacerbations and deterioration in lung function. An American study associated its acquisition by 58 of 308 patients with greater use of antibiotics and corticosteroids.[283] *Achromobacter xylosoxidans* is another such emerging pathogen. One concern about all these organisms is their intrinsic resistance to current antibiotics.

As discussed above, only limited information is available around lung infections in South Africans with cystic fibrosis. This study aimed to detail the time of acquisition of the two common bacterial infections in CF, *S aureus* and *P aeruginosa*, and the presence of other pathogens in the Western Cape province and to assess possible risk factors.

METHODS

Study population

All children on the RCCH CF database from October 1974 to September 2003 as described in Chapter 2. Children who had not had sputum cultures were omitted.

Study design

Retrospective folder review.

Data

Demographic variables: Ethnic group (see Chapter 3 for explanation of classification), sex, CFTR genotype (ΔF508/ ΔF508, ΔF508/Other, Other/Other).

Clinical variable: Pancreatic status (sufficient or insufficient)

Bacteriology:

1) *P aeruginosa* and *S aureus*

The age at which either of these organisms was first detected in respiratory secretions was recorded. These samples were collected during inpatient or outpatient care. Over the years, samples were either taken owing to clinical symptoms or, in more recent years, for surveillance. At no time was there a systematic regime for surveillance of sputum cultures in the CF Service. Samples were either produced by coughing (older children) or

by deep pharyngeal suction after physiotherapy (younger children and infants). Occasional samples were from tracheal aspirates (intubated children in intensive care). Microbiological methods were those extant in the laboratories at the time. Over the whole period, plating allowed for detection of both of these organisms.

2) Other organisms

The presence of other bacterial organisms associated with CF was noted and the age at infection recorded. Routine culturing for fastidious organisms such as *B cepacia* began in the 1990s. Culture for mycobacteria was only performed if requested by the clinician. *Aspergillus fumigatus* was not studied.

Analysis

P aeruginosa and *S aureus*: Simple proportions of infected children in the population were calculated. Time from birth to first infection was analysed according to the Kaplan-Meier method with incomplete data being censored at the time of the last visit or death. Those in whom the interval between respiratory tract samples made accurate assessment of time of first infection impossible were excluded from any time-dependent analysis. The analysis was repeated excluding children who were already infected at the time of diagnosis or within two months thereof. Time to first infection was compared between demographic variables using log-rank statistics (StatSoft, Inc. (2004). version 7. www.statsoft.com). The proportions of patients who acquired *P aeruginosa* without or before *S aureus* were calculated.

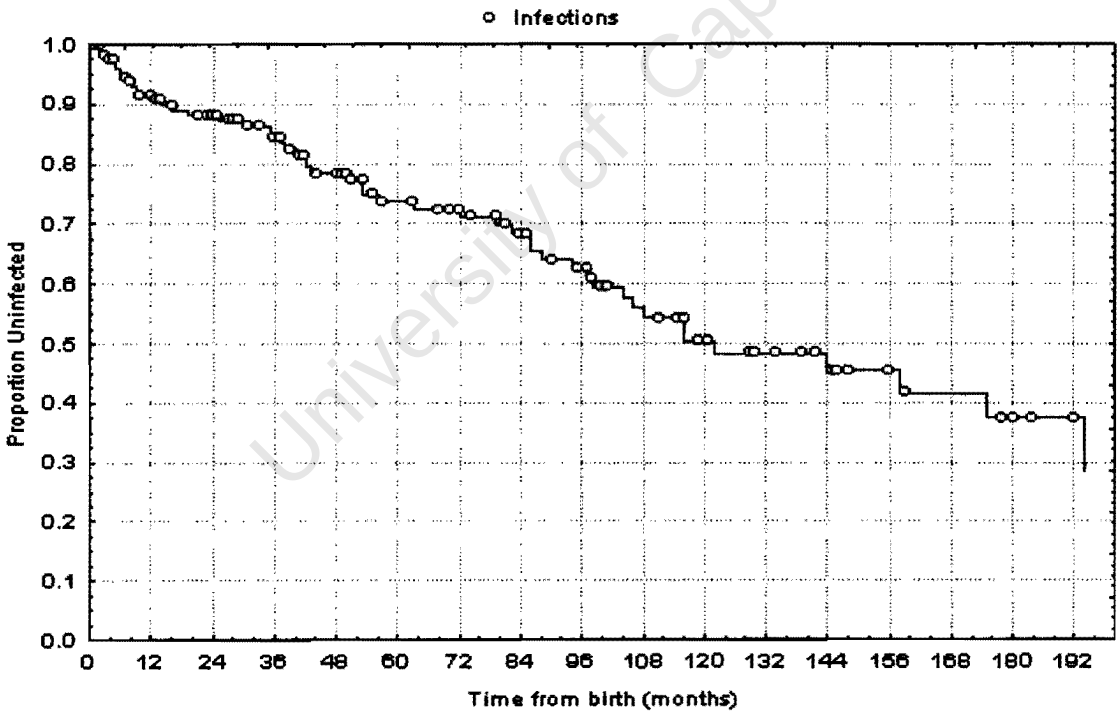
RESULTS

One hundred and eighty one children entered the study. For 177 of the 181 patients there was sufficient information to indicate whether they had ever been tested for bacterial respiratory infection. Their ages at last follow up ranged from 2 months to 26 years and 6 months (median 8 years and 10 months). In all, 118 (66,7%) patients had been infected with *S aureus* and 110 (62,1%) had acquired *P aeruginosa*. Twenty four (13,6%) patients had never grown *P aeruginosa* or *S aureus* (median age 48 months, range 3 months - 23 years and 10 months); 81 (45,7%) had grown both pathogens; 37 (20,9%) had only ever

grown *S aureus*; and 29 (16,4%) had only grown *P aeruginosa*. Twenty two of the 81 children who were co-infected with the two organisms were infected with *P aeruginosa* before *S aureus* appeared in their lung secretions. One of the nine pancreatic sufficient patients had acquired *P aeruginosa*.

In 159 cases there was sufficient information to determine the timing of the first *S aureus* infection. The median age was 117 months (interquartile range 53 - 197 months) when those already infected at diagnosis are included. If such cases are excluded, median age at acquisition was almost the same: 118 months (141 cases). Figure 7.1 shows cumulative time to *S aureus* infection for all 159 cases. There was no difference between the ethnic groups (p = 0,96 log-rank test) or sexes (p = 0,98 log-rank test). The three genotype groups had similar risks for acquisition of *S aureus* (chi square = 0,113, p = 0,94).

Figure 7.1 Cumulative time to infection with *Staphylococcus aureus*



The median age at acquisition of *P aeruginosa* was 150 months (interquartile range = 98 – 239 months) if those already infected at diagnosis were included (173 cases) (Figure

7.2). If such cases are excluded, median time to acquisition of *P aeruginosa* was higher at 185 months (interquartile range 116 – 251 months) for the remaining 146 cases. In view of the large number of cases already infected when the diagnosis of CF was made (27 cases), analysis of time-dependent data excludes these subjects. There were no differences in time to acquisition of *P aeruginosa* by ethnic group (p = 0,66, log-rank test, Figure 7.3), or by sex (p = 0,97, log-rank test).

Figure 7.2 Cumulative time to infection with *Pseudomonas aeruginosa*

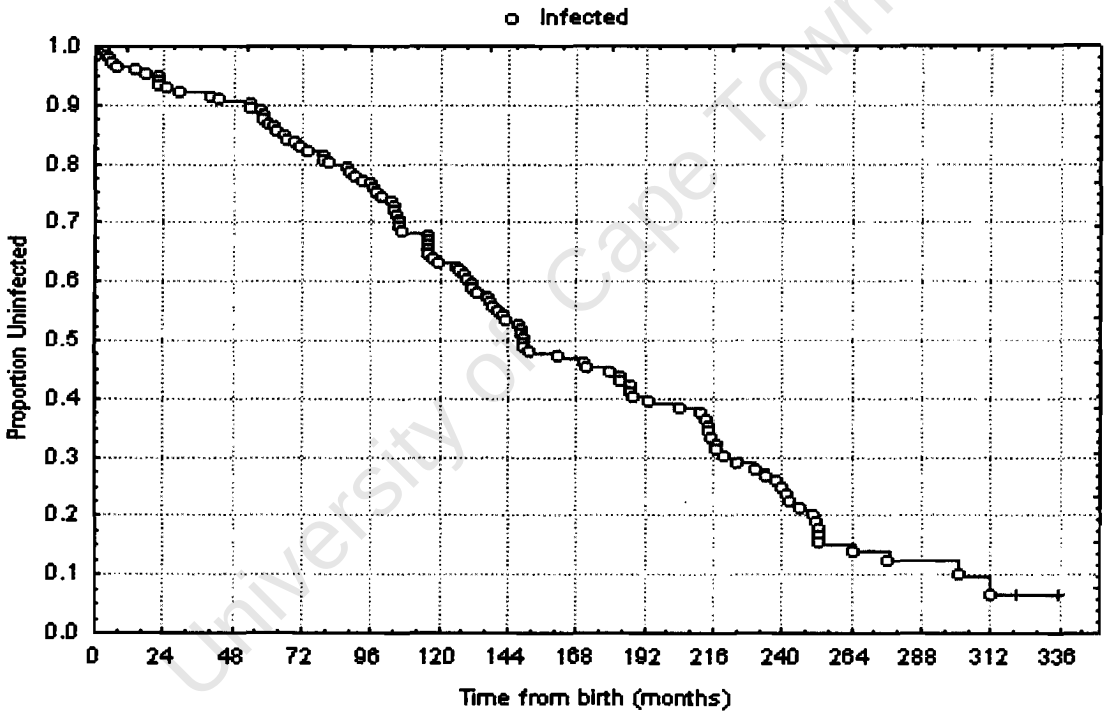
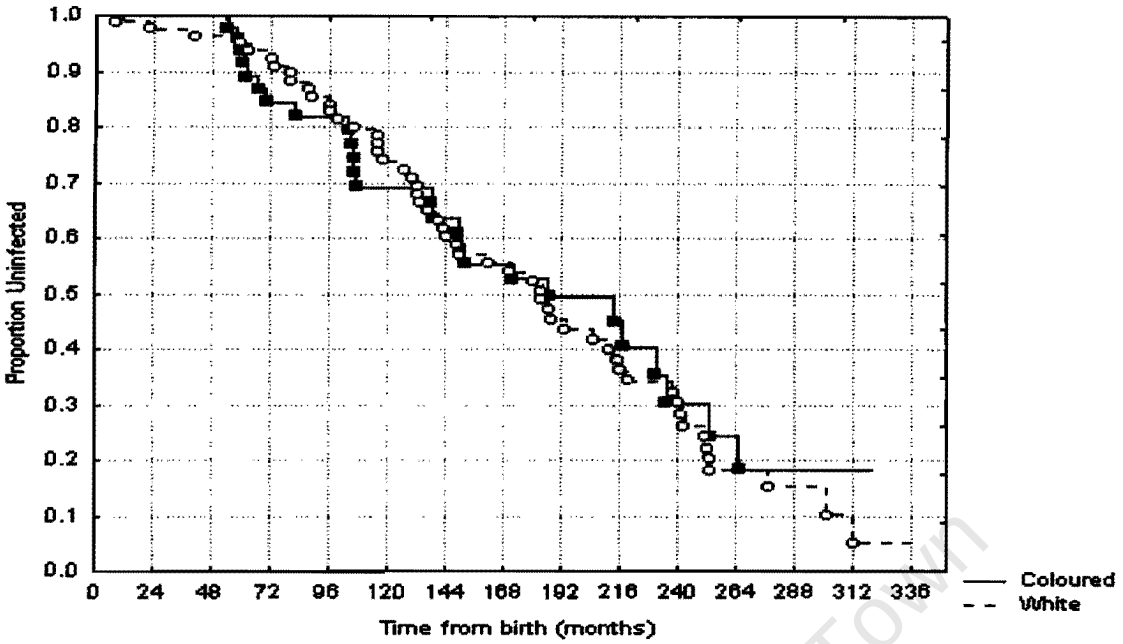
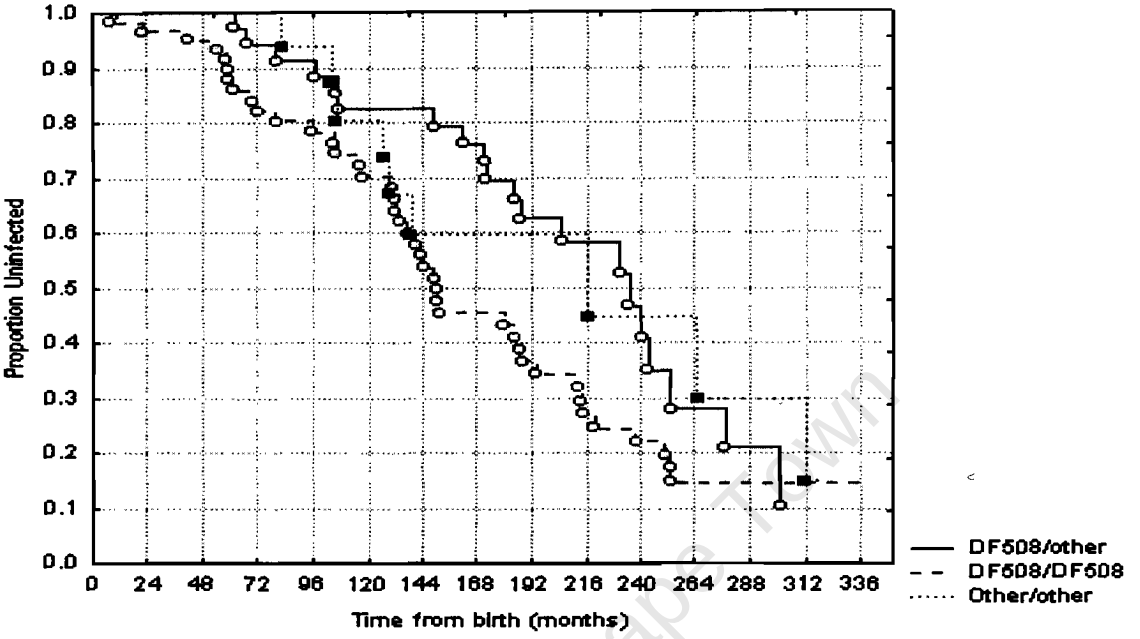


Figure 7.3 Cumulative time to infection with *Pseudomonas aeruginosa* by ethnic group



Acquisition of *P aeruginosa* occurred significantly earlier in patients who were homozygous for ΔF508 (chi square = 7,5, p = 0,023, Figure 7.4). This difference is emphasised when only coloured patients (N = 50) are considered: chi square 12,2, p = 0,002. The distribution of the 6 pancreatic sufficient patients who had had sputum samples sent, only one of whom, a white patient, had acquired *P aeruginosa*, was more or less equal between the two groups (4 coloured, 2 white).

Figure 7.4 Cumulative time to infection with *Pseudomonas aeruginosa* by genotype



B cepacia was identified in three patients, all in the 1990s: a 15 years old boy from whose sputum the organism was grown only once but whose lung function deteriorated rapidly from then on; an 8 year old girl with stable lung function who was referred from Port Elizabeth already infected and moved, still well, to Durban two years later; and, a single isolate in a 9 year old girl in the terminal phase of her CF lung disease.

S maltophilia had only been grown once in this population. A 5 year old boy, already colonised with *P aeruginosa* had the organism in his sputum for a few months. Antibiotic therapy was given and it cleared. A 6 year old girl was the only child to have proven infection with a non-tuberculous mycobacterium. No action was taken as specific symptoms were not attributed to the isolate. Two patients had tuberculosis identified. One boy who was pancreatic sufficient had severe pulmonary tuberculosis before the diagnosis of CF was made in his teen years. This infection significantly worsened his lung function. A second child was identified to be infected with *M tuberculosis* at *post mortem* but had been asymptomatic for tuberculosis when he died of a Reye-like syndrome at 14 months of age.

DISCUSSION

This study represents the first detailed examination of the microbiology of CF lung disease in a South African CF population. While it provides some insights into the prevalence and chronology of bacterial lung infection, the chief drawback of the study is the lack of systematic sampling of lung secretions. Only in recent years have samples been obtained with any frequency between pulmonary exacerbations. The figures presented thus represent the time to *recognition* of these infections rather than the true time of infection. Further insight into the actual time of infection by *P aeruginosa* might have been gained if the laboratory had routinely reported the phenotype of the isolate as non-mucoid strains can usually be assumed to have been present more recently than mucoid strains. This lack precludes any further inferences regarding the relationship between the time of recognition of *P aeruginosa* infection and the true time of first infection. It also makes the distinction between first infection and true colonisation difficult as children may have been colonised with *P aeruginosa* by the time the first isolate was detected.

What can be learnt from these data? The overall picture is much as expected. Infection with *S aureus* occurred earlier than with *P aeruginosa*, but was not a *sine qua non* for the latter. Some patients were able to live for many years without acquiring these infections. However the median age of the uninfected group was less than 5 years, a long way below the median age of infection in the rest of the population. Many of them are likely to acquire infection as they grow older. Only six of these 24 patients had lived infection-free beyond the median age of infection by *S aureus* i.e. 118 months. Two of these were pancreatic sufficient. Pancreatic sufficiency was shown by workers in Hanover, Germany to protect against *P aeruginosa* infection: such patients were 5,6 times less likely to acquire the infection than those deficient in pancreatic function.[284] Likewise in Toronto, three of five patients surviving with no evidence of *P aeruginosa* infection to 37 years of age were pancreatic sufficient, a proportion beyond that which could have been expected by chance.[285] Thus, in this CF population, infection with either or both of these organisms in childhood was the norm.

More specific comparison of the proportion of children infected with the two organisms with other CF centres is not possible as other reports are cross sectional as in those from the North American CF Foundation's Patient Register,[140] describe populations in whom surveillance of respiratory secretions was done[260 276 277] or study populations in whom there are decreasing rates of infection over the period in this study.[278 286]

The time to first *P aeruginosa* infection in the non-screened CF population has been well shown by the CF Clinic in Copenhagen, Denmark.[287] Routine regular culture of respiratory secretions has been practised there since the mid-1970s. A median of 4,35 years has not changed in 20 years despite changes in clinical practice, including cohort segregation by *P aeruginosa* infection status. The median age of over 12 years shown for the Western Cape province is therefore very likely to reflect delayed recognition brought about by waiting for clinical symptoms. It should also be noted that a significant proportion of our children (10%, Study 9.2 p259) had died before reaching the four years of age median for *P aeruginosa* acquisition. Since eradication of early non-mucoid *P aeruginosa* infections has been shown to be possible, the practice of surveillance, introduced in our service in the 1990s, is more than justified. (Preliminary data from this changed approach is presented on p213.)

While the Danish study gives the most consistent results for time to first acquisition for the whole of our study period, it is important to consider data from other centres as ecology and epidemiology may vary between geographical sites. As discussed in the literature review, recent studies using BAL and serology have established a very early time of infection in two sites on two continents. It is likely that this is the norm and studies that depend on oropharyngeal or sputum specimens do not reflect the true state of affairs. Nonetheless such studies do give a perspective more related to clinical decision-making. Time to acquisition of *P aeruginosa* when studied by these methods varies greatly. If the median age in Denmark was 4 years,[287] it was 15 years in a non-screened population in Hanover, Germany[284] and 8 years in a screened population in Colorado, USA.[260] The mean age in Manchester, UK (unscreened) was 11 years[247] and the median

age in Wisconsin, USA (screened) was either 1 years or 5 years, depending on the CF centre.[277]

The RCCH median of 150 months (12 and a half years) to infection with *P aeruginosa* included many patients who were infected at the time of diagnosis. The considerably higher median when these patients were excluded (15 years and 5 months) indicates that such patients were young. It can thus be said with confidence that most patients in this study were infected with *P aeruginosa* well before 12 years of age.

The data regarding demographic and genetic risk factors for acquisition of *S aureus* are consistent with the literature in that none have been described. The lack of difference in time to infection with *P aeruginosa* between the two ethnic groups in this population contrasts with the earlier acquisition in coloured patients (median 1 year versus 4 years for white patients) identified in the 1999 study of the prognosis of CF in this province (Study 9.1).[52] The number of CF patients in the database has increased by nearly 80% since then with the proportion of coloured patients increasing (29% to 43%, see Chapter 2 p21). To explain this change infection (or detection) must have been occurring later since 1994, the last year that children were enrolled in that study,. Detection might have been expected to have occurred earlier in recent years owing to better surveillance. Thus it is likely that time to infection has been longer in coloured children in the years after 1994. My suspicion is that coloured infants have not been as sick and have spent less time in hospital in recent years. They thus have less nosocomial exposure to *P aeruginosa* but, being healthier, they also will have had fewer specimens of sputum sent in the very early years of life.

No differences for time to *P aeruginosa* acquisition between the sexes were found. Given small numbers and the relative narrowness of the gap between girls and boys shown in the studies that have shown female sex to be a risk factor,[260 273] such a finding does not exclude a difference.

That the homozygous ΔF508 genotype has led to earlier acquisition of *P aeruginosa* is consistent with the apparent affinity of the mutation for epitopes of the organism as shown by Zar and colleagues.[262] It is also consistent with Maselli and colleagues' recent prospective study of infection in CF where ΔF508 homozygosity conferred a 123% greater risk for infection.[260] That this phenomenon is demonstrable in the coloured patients but not the white ones is probably a mathematical function of the greater proportion of non-homozygotes among these patients.[48] Studying a Quebecois population in Canada, de Braekeleer and colleagues were unable to distinguish a particular risk from ΔF508 homozygosity but could demonstrate decreased colonisation in those with the A455E mutation, a variant that is associated with the retention of pancreatic function.[288]

The comprehensive Danish study of *P aeruginosa* infection over two decades recorded the effect of cohort segregation on rates of chronic infection.[287] Introduced because rates of first acquisition rose following the introduction of regular admission for intravenous antibiotics in patients with *P aeruginosa* infection, probably through cross-infection, it was associated with a very large drop in rates of chronic infection. While controversy still exists regarding the role of cross-infection in CF, it is important to state the context of our results in this respect. Cohorting, apart from patients infected with *B cepacia,* has never been practised at the RCCH. Patients all attended the same clinic in the hospital's Physiotherapy department, and waited in the same area. Admissions have been to the same ward, though small patient numbers have meant that it has been unusual, especially in the latter years of the study period, to have more than one patient admitted at a time. Pulmonary function testing, only regularly performed since the early 1990s, has been subject to strict infection control. Rates of *P aeruginosa* infection have now been shown to be greater in CF centres. Comparing patients attending an established CF centre and those from a regional hospital, Mahadeva and colleagues found earlier acquisition of *P aeruginosa* infection in the former group (mean: 11 versus 16 years), although clinical outcome was better at the established centre.[247] The Wisconsin prospective study of newborn screening found a lower age at acquisition of *P aeruginosa* in children from the more rural site in the state (median: 52 versus 289 weeks).[277] Fewer social contacts

between CF patients were thought to explain this, especially as allowing for differences in respiratory therapies did not remove the increased risk in the urban setting. The role of cross infection in our service up till now is difficult to judge. A more detailed and rigorous review of the possible contribution of cross-infection in our setting would be difficult given small numbers, a predominance of urban patients and limited laboratory resources. Staff and space constraints have not allowed segregation in our context. In Geddes' view, the case for general application of segregation has not yet been made:

> There are risks in doing too little but it may be worse to do too much.[289]

This study gives a first view of the place of unusual pathogens in CF in SA, and it appears to be a small place. *B cepacia* has been sought routinely in sputa from CF patients by the microbiology laboratory since the early 1990s and was only found in three patients. The view from other centres in the country is consistent with this low prevalence (personal communications, members of the Medical and Scientific Advisory Committee on CF in SA). This was a young population. Infection with *B cepacia* is thought to reflect the ecological pressure of repeated courses of intravenous antibiotics and thus its appearance would be expected to rise with age. However there must be other factors that lead to infection: Toronto, Canada has had a much higher prevalence than Copenhagen, Denmark (39% versus 3%) despite the systematic 3-monthly use of intravenous antibiotics for those infected with *P aeruginosa* in the latter centre.[285] The rapid decline in lung function associated with this organism may have occurred in one case in our series but it is difficult to prove since only one sputum sample yielded the organism. The strains that produce such rapid progression of lung disease are often epidemic, a phenomenon Cape Town has been spared. *S maltophilia* and non-tuberculous mycobacteria have only appeared as curiosities in this population so far. Only one patient had symptomatic tuberculosis. Cape Town is a high prevalence area for tuberculosis, but one in 177 cases over 29 years cannot be said to represent an unusually high (or low) incidence of tuberculosis in CF. The child probably suffered aggressive disease because he was on steroid therapy for 'asthma' at the time.

This report provides evidence that the past approach to sampling of respiratory secretions was inadequate for early identification of *P aeruginosa* infection. Regular surveillance of lower respiratory tract secretions will be required in future, especially in the youngest children who recent research shows are becoming infected at a greater rate and earlier than had been understood.[261 271] It is important to have accurate data on this subject; it cannot be assumed that SA will have the same pattern of infection as other centres given the county's ethnic and socio-economic uniqueness. Now that there are therapeutic techniques for postponing *P aeruginosa* infection using inhaled and oral antibiotics as demonstrated in Denmark,[290] it will be important to continue monitoring lung infections in SA, both to identify first infections and the return of the organism after apparent eradication with antibiotics and also to monitor the efficacy of our regimes.

Further study of respiratory health in cystic fibrosis in South Africa. What are the options?

The studies reviewed and reported here have given a limited insight into the respiratory health of patients with CF in SA. If Zar's study of lung function and this study of respiratory pathogens are the start of a quest to know more about this subject, what should follow? The rationale for clinical studies must always be the well being of patients, present and future. In the clinical setting, audit is a mandatory form of study that should be patient-centred. The least our services should be doing is monitoring their effect on patients and adjusting practices in a continuous cycle of evaluation and change, but what is the role of measures of respiratory health in this process? In the case of CF, lung health has best been defined by measures of lung function. Unfortunately pulmonary function tests, while very useful in monitoring the respiratory health of an individual with CF, are a much blunter instrument in measuring populations or the effects of new therapies or changes in service delivery. Cross sectional data such as that produced in Zar's study would be more useful if related to age and compared over time. Even better, longitudinal data could be recorded and analysed. The limitations here are both practical and statistical in our context. Pulmonary function testing has only been performed regularly for just over a decade. With a clinic size of about 80 young adolescents and children, with a proportion of these being below an age at which a

reasonably reproducible forced expiratory manoeuvre can be expected, limited numbers of children would be found in each age bracket (however defined). This would significantly reduce the power of any statistical analysis. Moreover annual declines in $FEF_{25-75\%}$ averaged about 8% per annum in the developed world at a time when the outlook for CF was about where it is in SA now[291]; and the healthier patients who are benefiting from the most recent advances in therapy may have declines in FEV_1 of as little as 2-3% per annum.[257] Long time spans would be required to measure the effect of service or therapeutic change in this population. Table 7.2 gives data from an analysis of pulmonary function tests from the 1990s to the present in this population at ages 5 years apart to illustrate this difficulty. While mean FEV_1 is seen to decrease with age, the range of the readings increases producing very high standard deviations. The number of subjects decreases dramatically in the teenage years, a fact much more stark in its implications for health services than the lung function deterioration in the survivors. An attempt to follow the fortunes of females or coloured patients, both vulnerable groups in CF, is shown in Table 7.3. Are female and coloured 16 year olds really worse off as suggested by the basic data in Table 7.3 or is it merely the presence of one coloured female patient with FEV_1 of 15% that produces such a poor mean? Sadly, small numbers and wide ranges within each group again preclude any definite conclusions about the effect of sex or ethnic group on lung function in the Western Cape province.

Table 7.2 Percentage expected FEV_1 at ages six, eleven and sixteen years

	6 years	11 years	16 years
N of subjects	23	25	10
Mean	92.9	85.8	63.7
SD	12.3	20.3	26.9
Median	97	86.5	64.5

Table 7.3 Percentage expected FEV_1 at ages six, eleven and sixteen years by sex and ethnic group

	6 years				11 years				16 years			
	Male	Female	Coloured	White	Male	Female	Coloured	White	Male	Female	Coloured	White
Number	12	11	10	13	16	14	12	18	7	3	3	7
Mean	90.7	94.8	93.9	92.1	88.4	82.7	85.7	85.8	69.9	49.3	49.3	69.9
SD	11.5	13.2	12.7	12.5	20.1	20.8	14.8	23.6	18.8	41.9	41.9	18.8
Median	95	100	100	95	87	86.5	86.5	87	65	37	37	65.5
Range	63-105	82-115	66-108	63-114	67-115	30-127	54-100	30-127	37-106	15-80	15-96	46-106

Longitudinal data suffers from similar weaknesses. In just over a decade few children will have aged enough for the small number of values available in this population to give a meaningful picture of decline in lung function. Even the complexities of the mixed model analysis that is now advocated for such longitudinal studies[257 292] are unlikely to be able to compensate for this. Longitudinal data covering periods of 5 years (6 to 11 years, 11 to 16 years) was only available for 14 children in this population.

Respiratory health in CF depends to a great deal on the control of *P aeruginosa* infection and the associated inflammation. The RCCH CF Service has tried to keep abreast of advances in this area. An example was the demonstration by Valerius and colleagues in 1991 that a regime of antibiotics might postpone chronic infection by *P aeruginosa*.[21] Our first patient to have an attempted eradication was admitted to hospital in 1993. Subsequently 20 patients have had such attempts. Such regimens involve a lot of input from parents and the health service and have unknown risks and therefore are ripe for audit. I reviewed these 20 patients (23 eradication attempts). Regimes instituted included admission for IV therapy when the children were symptomatic sometimes followed by inhaled gentamicin, or oral ciprofloxacin for 3 to 6 weeks associated with 3 to 6 months of inhaled gentamicin. Delay in noting the positive laboratory result happened twice. The medication was not written up for one patient. One patient had only oral ciprofloxacin for three months. All others did receive either IV antibiotics with or without follow up inhaled gentamicin, or a combination of oral and inhaled antibiotics. In one case too few sputa were sampled to be sure that eradication had taken place. In two cases the child had grown *P aeruginosa* years before which had cleared. Chronic

infection at its reappearance was not prevented in either case. Eradication (defined as no growth of *P aeruginosa* one year after initiation of the regimen) was achieved in 8 of the remaining 16 completed first attempts (50%). However on an intention to treat basis the proportion with a successful eradication was 38,1% (8/21). This audit identifies problems with implementation that require review of procedures for capturing results and acting on them. It also demonstrates that the effort is probably worthwhile. If this regimen were to be combined with greater attention to surveillance of lower respiratory tract infection as advocated above, benefits in line with those demonstrated in Denmark[290] may accrue to this population.

Recently alternate month (as opposed to continuous) gentamicin therapy and thrice weekly azithromycin therapy have been introduced in the CF service for patients with chronic *P aeruginosa* infection. In these cases, audit can only measure how well we are implementing our policy on suppression of *P aeruginosa* chronic infection as measurement of outcomes is very difficult since it depends on lung function (only small but 'significant' changes were demonstrated in the studies that have shown the benefit of these regimes, about 6% increase in FEV_1[20 268]) and patient well being.

Another measure of respiratory health in a South African population might be days in hospital or courses of intravenous antibiotics for pulmonary exacerbations. Unfortunately regimens have varied over time and the public/private mix of patients makes accurate measurement difficult. It is my impression after 16 years of interaction with CF patients on IV therapy in the Western Cape province that children's respiratory health as measured by number of courses of IV therapy has improved in that time, despite a more aggressive approach to treating *P aeruginosa* infection and declines in pulmonary function measures. It may be possible to measure such trends prospectively by routine data collection. This could coincide with the tightening up of the other approaches to maintenance of respiratory health in this population discussed above.

It must be noted that while these new antibiotic regimes have entered routine CF care, a number of other changes have occurred simultaneously:

More aggressive nutritional care (see Chapters 6 and 8)

A greater range of physiotherapy techniques

Routine influenza vaccination

Multidisciplinary care (see Chapter 8)

An emphasis on general physical fitness and exercise[250]

Systematic and routine data collection has the potential to assist in the evaluation of the overall effect of these modalities of care. Despite the caveats expressed above regarding lung function testing, it would seem that the Western Cape province has not reached a point where the lung function of young CF patients and mortality[52] no longer reflect where change is occurring. It is my view that changes (or lack of changes) in decline in lung function over time (and in mortality, see Chapter 9) still have the potential to tell us about the degree of *access* to *efficacious* CF care that patients with CF are receiving in SA, especially in the Western Cape province with the unique socio-economic challenges that face many of its CF patients.

CHAPTER 8

HEALTH SERVICE ASPECTS

OUTLINE OF CHAPTER

This chapter will describe what is required of health services for a long term health condition like CF. Some aspects of how the RCCH CF Service has endeavoured in recent years to provide a progressively improving service to meet the changing needs of patients with CF will then be detailed. Transition to adult care is the subject of the main study described in this chapter. The chapter ends with consideration of End-of-life care in CF.

INTRODUCTION

Achieving optimal health status for almost all patients with CF is dependent on an extensive use of health services. While health service interventions such as surgery and inpatient care may be needed, the main purpose of health care in CF is surveillance, anticipatory guidance and early intervention. This is particularly the case for younger persons with CF as modern CF care has led to the postponement of severe complications to later life for many of them. Surveillance includes close monitoring of physical growth, lung symptoms and function, patient understanding, and monitoring for complications. Anticipatory guidance covers reproductive choices and genetic counselling, seeing the child and family through life's milestones and the development of the manifestations of CF that come with time. Early intervention includes recognition and management of deteriorating nutrition, lung infections and complications of CF as well as psychosocial consequences of the disease. These are all classic parts of preventative medicine; they are the backbone of CF care. Without them the patient and family would stumble from crisis to crisis or progressive deterioration would take place unnoticed leading to much worse health status and outcomes.

Research and experience have shown that this form of CF care is best led by centres of expertise in CF care. This was shown very effectively by a study of patients in East Anglia in England.[247] Centre care was compared with that in a regional hospital and that away from hospital care. Patients attending the centre had better health status. The only identified drawback was an higher rate of *P aeruginosa* infection among patients who attended the CF centre. The CF Service at the RCCH is such a service. Established in 1973 it has concentrated expertise in a team, mainly medical to start with but now multidisciplinary, that has offered expert outpatient, inpatient and emergency care in a tertiary health care setting to any patient with CF in the western Cape Province.

Cystic Fibrosis as a Long Term Health Condition

The last three decades have seen a large growth in chronic diseases of lifestyle among adults. The large numbers of older persons with often multiple ongoing disorders have challenged health services to respond to a very different set of health care needs from persons with acute health problems. For children there has also been a recognition that numbers of children with health conditions that are not cured but controlled are rising. Children's health services in developed countries (where the proportion of children seeking curative health care for acute conditions has dropped) have begun to adjust to this. A whole edition of *Pediatric Clinics of North America* was dedicated to this phenomenon in 1984. In an oft-quoted paper, Gortmaker and Sappenfield spelt out the size of the issue of children with chronic conditions.[293] Unlike with adults, chronic conditions in children are more often genetic than degenerative. Cystic fibrosis, one of the commonest single gene disorders, merited a chapter of its own.[294]

Stein and other workers in the USA have made an extensive study of the issues health services face in providing appropriate care to children with 'long term health conditions', a term they coined.[295] Such a condition is defined as follows:

A disorder that

1. has a biologic, psychologic or cognitive basis, and
2. has lasted or is virtually certain to last for at least a year, and
3. produce one of more of the following sequelae

a. limitation of function
b. dependency on medications, special diet, medical technology, assistive device, or personal assistance
c. need for medical care or related services, psychologic services or educational services over and above the usual for the child's age

Essentially such conditions threaten normal development of the child, both physically, emotionally and socially. Health services need to be able to optimise the child's development and prevent secondary disability (e.g. emotional or behavioural disorders). These needs are 'non-categorical' i.e. they do not depend on the individual health condition, rather it is the fact that the condition is long term that dictates the child's potential special health care needs.

Cystic fibrosis in an incurable, genetic, progressive, multi-system, life-shortening disorder. Each of these characteristics brings with it a multiplicity of challenges and risks for the child and family to which health and other services should respond. Its incurable nature means that there is no life without CF. Psychological adjustment for child and family must be promoted; life's milestones must be anticipated and the potential effect of CF at these points discussed with the child and family. Its genetic cause impacts on reproductive choices for child and parents and extended family. Its progressive nature brings a constant battle to maintain health through complex health promoting and disease modifying medical interventions, each of which may impact on the child and family's lifestyle and choices. More battles are lost than won with CF; health care and other services needs to be able to deal with this and help the family deal with this. Its multi-system nature makes it medically complex, requiring highly specialised health care often concentrated in a health service far from the family home. Its life-shortening nature is known from the time of diagnosis. The psychological impact of this fact is ever present with the family and health care team.

THE RED CROSS CHILDREN'S HOSPITAL CF SERVICE

I have been closely involved with the RCCH's CF Service since 1992. The prior work of Malcolm Bowie, Robert MacDonald, Ivor Hill, John Ireland, Mike Gold,

Colin Wallis, Lesley Henley, Shanaaz Matthews, Lorna Gale and others over two decades had led to a high standard of service. A weekly clinic took place in the Physiotherapy department on Tuesday afternoons. All doctors were attached to the hospital's Gastroenterology Service. Patients were discussed by the doctors after the clinic. Lung function testing was done at the Allergy Clinic by the Respiratory technologist. Pulmonology Services were only available on a consultation basis. A dietician (the only one employed by the hospital!) attended the Clinic when she could and a social worker was available. The head physiotherapist gave input if requested to. Inpatient care was concentrated in Ward B2 and a 24 hour consultation service was available. A service for adults with CF already existed in the Respiratory Clinic at GSH.

When John Ireland took over as head of the Service on Malcolm Bowie's retirement in 1994, a pulmonologist (initially Andrew Argent) was invited on to the team. A junior physiotherapist became part of the team as did a dietician once the hospital staff complement increased to two. Another innovation was a weekly meeting of *all* members of the therapeutic team. This added greatly to the depth of assessment and planning of care for individual patients and to protocol development and service development. A new clinic form was introduced to improve systematic clinical care and anticipatory guidance. The form, which had features that aimed to allow better longitudinal monitoring and contained prompts for the clinician has been adapted a few times at the suggestion of team members. It is reproduced as Appendix B. With the loss of the Respiratory technologist to a Severance Package in the mid-1990s the physiotherapist took over the lung function testing on a machine that had been donated to the Service by Round Table, Somerset West at the instigation of the parent of a child with CF.

A nurse joined the team part time in 2000 but this proved difficult to sustain owing to staff rotations and nurse shortages. The potential of this cadre has yet to be met in Cape Town despite repeated motivations.

The team has continued to produce leaders in CF care in the country (and beyond). Members regularly participate in SA's CF Symposia as speakers and John Ireland and I have been members of the Medical and Scientific Advisory Committee of the SA CF

Association. The team wrote a nutrition booklet for patients and parents to use[250] and contributed to two editions of the national Consensus statement on CF care in SA. The team has been aided in its work by the local branch of the CF Association and individual parents. For example, in recent years a donation has been made to help poorer children attend the clinic by supplying their parents with taxi or bus fare.

There are factors that the team feels undermine its work. Policies on state funding of patients with expensive and complicated conditions such as CF has changed to the detriment of patients in the last decade. Free care for CF was removed in the early 1990s.[296] [It must be acknowledged that the dispensation had only existed because most CF patients were white.] Free care for children under 6 years of age introduced in 1994 did not cover 'private' patients. More and more, private patients have been expected to fund their own care despite it being patently obvious that this is unaffordable for most. Hospital budgets have progressively shrunk. New therapies such rhDNase have only been used in exceptional circumstances because of their cost. Even mainstream therapies are under constant scrutiny by hospital administrators. The team has fought a number of rearguard actions to maintain good standards of care for patients.

The research described in the preceding chapters has been part of the Service's audit process. We wished to ensure that steady improvement of health status continues as it has been in developed countries. We wished to know if there were local differences in CF manifestations that should influence how we adapt CF care to our unique circumstances.

There are two health service aspects of clinical care of CF that have also been studied as part of our self-assessment: transition from paediatric to adult-oriented CF care and End-of-life-care.

TRANSITION FROM PAEDIATRIC TO ADULT-ORIENTED CYSTIC FIBROSIS CARE

Transition has become a buzzword in health services and related medical literature. In relation to health, it refers to the process of change from paediatric to adult-oriented

health care. Its particular focus is on children and young persons with long term health conditions. Transition has risen to prominence in recent years owing to the success paediatric health care services have had in prolonging the healthy lives of children with many health conditions that used to be associated with death in childhood. CF is one such condition.

This phenomenon of an increasing number of CF patients passing through childhood, then adolescence to adulthood became part of life in Cape Town in the 1980s. The increasing demands placed on the RCCH CF Service by older patients led to Prof. Bowie negotiating the establishment of a CF service for adults at GSH. This officially opened its doors in 1989 although a few adults with CF were already attending the hospital. The new clinic underwent some rapid changes of staff in its early years and only stabilised when Dr Paul Willcox returned to the Respiratory Service at GSH. Back on the RCCH side, I was rapidly learning that CF among adolescents presented challenges I had not encountered before. I noted that many did not attend regularly, were often at odds with their parents and had a different relationship with health care professionals from younger patients. A particular concern seemed to be their and their parents' negative attitude to moving to GSH. This appeared to be having a deleterious effect on the young people's health in some cases.

Fortunately for me, Dr Lesley Henley, a social scientist, was in the Department of Paediatrics and Child Health of the University of Cape Town. Although she was no longer part of the CF team, she maintained her interest in the health issues surrounding children with long term health conditions. My discussions with her led to a survey of the attitudes of the CF 'family' to growing up with the disease and changing health providers.

This section contains the paper that was one of the outcomes of this survey. This is preceded by a more detailed discussion of transition than was possible in the constraining atmosphere of a journal article. The reproduction of the paper that was published in 1999 in the *Journal of Paediatrics and Child Health*[57] is followed by an updated view of the CF-related transition literature and a description of our most recent attempts to improve transition for patients who attend the CF services.

Transition in Cystic Fibrosis: a literature review

Despite the dismal prognosis of CF in the 1950s not all patients died early. Issues arising out of the presence in health systems of survivors of the disease were recognised in the early 1960s. Shwachman and colleagues described 65 patients over the age of 17 years in 1965. They put this new phenomenon down to

> .... greater awareness of cystic fibrosis.....(i)mproved diagnostic techniques.....effective therapeutic measures, notably antibiotics.....mild manifestations of the disease....exist....[297]

The number of adults with CF has risen steadily since then in developed countries until the present day when about half of all prevalent CF cases are adults. Even in SA, adults were present in good numbers in the early 1980s[32] and, as described above, Cape Town also needed to deal appropriately with a steady stream of patients surviving beyond teenage.

With this excellent medical success story came a new challenge to health services. Who was to look after this new breed of adolescents and young adults? That new challenges were arising was noted in a short paper 'to alert the medical community to the need for a change in the type of service presently delivered to teenagers with cystic fibrosis' in the Annals of Internal Medicine in 1973.[298] Rosenlund and Lustig in Philadelphia, USA, the authors, had piloted a programme for older patients with CF, encouraging independence and dealing with psychosocial issues facing them.

This 'new breed' of survivors of severe paediatric disease was not unique to CF. In the 1980s papers describing the issues in cancer,[299] diabetes,[300] and renal disease[301] appeared. Gortmaker and Sappenfield demonstrated the high number of children with long term health conditions in the opening paper of an edition of *The Pediatric Clinics of North America* in 1984.[293] Interestingly this edition of the journal, while taking up many issues of 'chronic childhood disorders', did not take up the issue of transition. 1989 was the year transition came of age (so to speak!), at least in the USA. The Surgeon General, C. Everett Koop convened a conference on the issue. This moved transition into the mainstream of health policy. Blum gave an overview of transition

in 1991 in *Pediatrician*. Increasing numbers of children were surviving to 20 years and beyond; adolescents have special needs; they use health services more than their 'healthy' peers; transition, he stated, was 'more by default than by design'.[302] Soon after this (1993) The Society for Adolescent Medicine published a "Position Paper" in the *Journal of Adolescent Health*. Blum was the first author. This paper presented a definition: ....the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-centered health-care systems' that has generally been taken up by authors in the field in subsequent years.[303] It was acknowledged that much was unknown about the process. The need for the process to be studied and evaluated was emphasised. The Society wished to place transition on the research, service development and training agenda.

Apart from Cameron who wrote about renal disease,[301] the European literature was almost silent on this issue at this time. As we were preparing to launch our research into transition issues in our services, Landau, an Australian paediatrician, penned a lengthy and comprehensive editorial in *Thorax* (1995) about transition in CF.[304] Writing in an 'adult' journal he emphasised the qualities required by adult-oriented CF services that were required to ensure a smooth transition to good adult care in CF.

CF had been the subject of more transition articles than any other disease in the USA and Australian literature in the 1980s and early 1990s. One of the most perceptive articles, although it contained and referred to very little empiric or controlled data (because there was not much to be found), was written in *Medical Clinics of North America* in 1990 by Schidlow and Feil from Philadelphia, USA.[305] They spelled out factors that enhanced or hindered a successful transition. These factors related to each of the players in the process: the young person with CF; the parents; the paediatric team and setting; the adult team and setting (Table 8.1, taken from Table 2 in the article). This set a template on which much subsequent thinking and research has been based. Its American bias is given away by the prominence given to 'economic concerns' of caregivers in giving up or taking on older CF patients. Nevertheless, until later research (see below) suggested that the 'patient-related' factors had over-emphasised the adolescent's view of transition/transfer, this model rang true.

Table 8.1 Obstacles to Transition from Pediatric to Adult Health Care Systems (from Reference 305)

The patient	Dependent behaviour Immaturity Severe illness or disability Psychopathology Lack of support systems Lack of trust in caregivers Poor adherence to treatment regimes	**The Paediatric Caregivers**	Economic concerns about programme Emotional bonds with patient and family Comfort with status quo Perception of own skills as caregivers of adults Perception of potential survival of patients Distrust of adult caregivers Ambivalence towards transition and transfer of care
The family	Excessive need for control Emotional dependency Psychopathology Parenting styles leading to overprotection Heightened perception of disease severity Lack of trust in caregivers Mistaken perception of potential survival	**The Adult Caregivers**	Economic concerns Lack of understanding of congenital disease Lack of familiarity with disease entities Heightened perception of care demands Lack of institutional commitment

Rosen, in an article published in 1995 in the *Journal of Adolescent Health*, expanded on these themes by teasing out the cultural differences between paediatric and adult medicine that have the potential to trip up the young person on the transition path.[306] In essence, the paediatric environment is nurturing while the adult one expects independent behaviour of the patient. In the chronic illness arena, the former inhibits maturation; the latter expects too much maturity.

Sawyer and colleagues in Victoria, Australia conducted a series of studies of the insights young person with CF had into their disease and its effect on puberty, sexuality and reproduction and attitudes to caregivers.[307] It became clear that paediatric settings were not adequately conveying information important to the potential adult. This has implications for the efficacy of transition and adult coping.

Transition reached the mainstream (at least in paediatrics) when the American Academy of Pediatrics published statement of transition in *Pediatrics* in 1996. In essence, the Academy said:

- Begin early
- Promote independence
- Involve patient and family in the process
- Encourage patients acceptance

- Have adult and paediatric health care practitioner work together for a period[308]

It was in this year that we undertook our study, attempting to explore a number of these themes with a questionnaire aimed at CF patients and their families. Our particular focus was on attitudes to growing up with CF, transfer to adult-oriented care and need for knowledge of CF in adulthood. There was limited literature on these aspects at that time. Our study was largely undertaken to help us plan and adapt services in Cape Town. It is a comment on the relevance of the 'non-categorical approach' to chronic illness in children of Stein and colleagues that we were able to adapt a protocol used in sickle cell anaemia in the USA without much difficulty to our purposes with CF in SA.

Study 8.1

The Transition from Paediatric to Adult Care for Persons with Cystic Fibrosis: Patient and Parent Perspectives

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SUMMARY

Objectives: To gauge the perspectives of adolescents and adults with cystic fibrosis (CF) and their parents regarding the transition from paediatric to adult-oriented health care.

Methods: Cross-sectional survey using an anonymous, semi-structured questionnaire. The study population consisted of adolescents and adults attending a paediatric and an adult CF clinic in Cape Town, South Africa and their parents.

Results: Forty-seven of the 61 subjects completed the questionnaire (response rate 77%). Autonomy in health care was "extremely important" to most persons with CF. Transfer at the age of 16-18 years was the preferred option for most respondents. Whereas over 80% of parents felt their children needed more CF-related information, only 38% of adolescents expressed this need ($p<0.05$). Adolescents also reported little need for general health information. More than 80% of respondents were "unsure" about transfer. Over 90% felt that a transition clinic would be useful. As viewed by the respondents, its main purpose would be to provide information about the adult clinic and an opportunity to meet the CF doctor in the adult clinic.
Conclusions: There are significant concerns about the transition process in this population. Given the expressed need for autonomy and a transition clinic, the basis for a smoother transition in the future has been laid.

Key words: Adolescence, cystic fibrosis, health services; transition.

Cystic Fibrosis (CF) is one of many chronic life-threatening conditions in which the expected life span has increased considerably in recent years [1]. Median survival for persons with CF now extends to the third or fourth decade of life in many countries and the issue of how and where older CF patients are best cared for has evoked much debate. A particular concern is how best to manage the transfer from child- to adult-centred care as there are many potential service, patient and staff related pitfalls associated with the move [2-5]. This in turn has given rise to the concept of "transition" in which the transfer becomes part of a planned *process* of change in the orientation of care [4-7].

In Cape Town, South Africa where most persons with CF survive to adulthood [8], almost all CF patients attend public hospitals for their CF-related care. An adult-oriented clinic, but no formal transition process, was set up in 1989. Transfer from the paediatric CF Clinic at the Red Cross War Memorial Children's Hospital (RXH) to the adult CF Clinic in the Department of Medicine at Groote Schuur Hospital (GSH), a general hospital, necessitated a change in hospital and caregivers. The RXH Clinic which cares for about 75 patients is staffed by three paediatricians, a social worker, a dietitian and a physiotherapist. The GSH Clinic, with 20 patients, is run by a

pulmonologist and a physiotherapist. At neither clinic are the staff engaged in CF service full time.

In the years preceding this study, transfer occurred sometime in the adolescent or early adult years. Patients were given an appointment for the GSH Clinic and a summary letter from the paediatric doctor who had arranged the transfer. Problems surrounding the transfer from the RXH Clinic became clear as some patients and parents postponed transfer or failed to attend follow-up appointments. Such discontinuity of care threatened the adolescents' health and development.

As part of a remedial process and to identify areas in the clinical services which might benefit from organizational change, a survey designed to gauge the perspectives of adolescents and adults with CF and their parents was undertaken.

METHODS

Cross-sectional study data were obtained from four groups of subjects:

- adolescents with CF (ages 14-21) attending the RXH Clinic (Group RXH1)
- parents of children and adolescents (ages 10-21) attending the RXH Clinic (Group RXH2)
- adults with CF who had transferred to the GSH Clinic (Group GSH1)
- parents of adults with CF who had transferred to the GSH Clinic (Group GSH2)

Anonymous semistructured questionnaires were posted to all subjects during January 1996 followed by a second posting 3 months later. The questionnaires were sent to patients and parents in separate envelopes. Covering letters stressed the voluntary nature of participation.

The questionnaire was adapted, with permission, from a previous study [9, Telfair - personal communication]. Items on the revised questionnaire were pre-tested for clarity and local relevance. English and Afrikaans versions of the questionnaire covered:

1. demographics including a brief health self-assessment.
2. attitudes to growing up (independence, the need for information related to CF and lifestyle).

3. attitudes to the transfer (timing, feelings).
4. the transition process (needs, wishes).

Descriptive data were analysed using Epi-Info Version 6 (Centers for Disease Control. Atlanta, GA, USA). Where appropriate, the Chi-square test was used to compare groups.

Permission for this study was granted by the Research Ethics Committee of the University of Cape Town, South Africa.

RESULTS

Of those eligible, three adolescents were not sent questionnaires (two intellectual disability, one preterminal). Response rates were: RXH1 13/15 (87%); RXH2 21/26 (81%); GSH1 8/11 (73%) and GSH2 5/9 (55.5%). This reflects a total response rate of 77% (47/61). The mean ages of CF patients (50% female) were 16 years and 27 years at RXH and GSH, respectively. Five were employed and 13 were at school or university. Five patients lived away from their parents. Twenty-three percent of adolescents rated their health as "excellent" and 77% as "good". Adults with CF rated their health as "excellent" (25%), "good" (37.5%) and "poor" (37.5%).

Attitudes to growing up

Independence

Patients were asked to rate how important (response options: extremely important, quite important, not so important, not at all important) autonomy (independent and looking after yourself) was to them at their present age. Parents were asked to rate how important it was to them that their children exercised autonomy (independent and looking after himself). Table 1 shows the areas of autonomy included in the questionnaire and the proportion of respondents who considered them to be "extremely important". Unlike those who had transferred, adolescents did not consider "making their own clinic appointments" and "speaking alone to the doctor" to be very important. Moving to the GSH Clinic was considered to be "not so important" by 54% of RXH1 and 33% of RXH2 (their parents). Twenty-four percent of RXH2 felt that it was "not at all important".

TABLE 1

Areas of autonomy and the proportion of respondents who deemed "extremely important" (% distribution)*

	RXH1	RXH2	GSH1	GSH2
Making own decisions about treatment	77	57	75	40
Personally responsible for physiotherapy	46	62	87	60
Personally responsible for medicines	85	76	100	100
Making own clinic appointments	8	24	63	80
Speaking alone to doctor	31	43	87	80
Moving to adult CF clinic	8	19	-	-
Meeting other young people with CF	31	43	0	0
Taking charge of own life	61	67	87	80

RXH, Red Cross War Memorial Children's Hospital; GSH, Groote Schuur Hospital; CF, cystic fibrosis

Information needs

There were significant differences between parents' (RXH2) views of their childrens' information needs (response options: a great deal more, a little more, no more) and the adolescents' reported needs on subjects related to CF (Table 2). Most adolescents reported needing "no more" information on smoking and drinking (85%), puberty (69%), dating (69%) and contraception (69%).

TABLE 2

Information needs (% distribution)[$]	"A great deal more information" RXH1	RXH2
Complications in CF adults	38	90*
New developments in CF treatment	38	80[#]
Latest research findings in CF	54	80

*p = <0.002, [#]p = <0.02: RXH, Red Cross War Memorial Children's Hospital; GSH, Groote Schuur Hospital; CF, cystic fibrosis

Attitudes to the transfer

Timing

Respondents were asked what they considered to be the "best" age (minimum and maximum) for a young person with CF to transfer to the GSH clinic. In all groups a majority proposed 16 to 18 years (RXH1 65%, RXH2 61%, GSH1 75%, GSH2 80%). Two respondents did not proffer an opinion.

Feelings

Respondents were asked to rate the extent to which they shared a range of potential concerns related to transfer ("a big concern", "a slight concern", "no concern"). Table 3 shows areas relating to the transfer which were identified as "a big concern" by at least half of RXH1 and RXH2 respondents. When asked to choose from a list of possible reactions how they might feel about an imminent transfer, 86% (RXH1) and 85% (RXH2) of respondents reported being "unsure". The second most common feeling reported by all groups was "worried". Positive or neutral emotions ("excited", "okay about going", "it's the right time to move on") were indicated by fewer than 20%.

TABLE 3

Concerns about moving to the adult CF clinic identified by 50% or more of respondents from RXH
PARENTS (RXH2)
Not knowing what to expect
Paying for adult medical care
Is my child ready to be treated as an adult?
What do we do if we don't like the adult CF clinic?
How much do the adult caregivers know about CF?
Being admitted to an adult ward
ADOLESCENTS (RXH1)
What do I do if I don't like the adult CF clinic?
Not knowing what to expect
How much do the adult caregivers know about CF?

RXH, Red Cross War Memorial Children's Hospital; GSH, Groote Schuur Hospital; CF, cystic fibrosis

The transition process

Respondents were asked if it would be helpful to have a transition clinic at the RXH CF Clinic which the doctor from GSH would attend. All but 4 respondents (RXH 3, GSH 1) thought that it would be helpful to have a transition clinic. Respondents were asked to choose the kinds of help they would like from a transition clinic. Table 4 shows the possible functions of a transition clinic which appeared in the questionnaire and the proportion of respondents who would find those functions helpful. In response to an open ended question, further suggestions included a brochure about the GSH clinic and visits to GSH to see the clinic and ward. Two RXH respondents recommended a special adolescent CF clinic at the children's hospital.

TABLE 4

Help a transition clinic should offer (% distribution)	RXH1	RXH2	GSH1	GSH2
Provide information about the adult clinic	69	86	87	80
Opportunity to meet the new CF doctor	77	86	87	100
Opportunity for the new doctor to learn about me/my child	46	71	87	80
Deal with my worries about transfer	46	57	63	80
Opportunity for me/my child to meet others who are being transferred	46	52	63	60
Provide information about CF in adulthood	54	71	100	100

RXH, Red Cross War Memorial Children's Hospital; GSH, Groote Schuur Hospital; CF, cystic fibrosis

DISCUSSION

Requirements for and impediments to a successful transition from paediatric to adult care for persons with chronic health conditions have been the subject of many articles in recent years. Blum et al. [6], writing for the Society of Adolescent Medicine point out that, while many transition programmes exist, 'the failure to collect systematic data leaves us with only anecdotal evidence....' (p 573). Only three studies present data on transition in CF. Abdale *et al.* [10], examining satisfaction with the move from a paediatric hospital to an adult centre amongst adults with CF found that, of the 63% who responded, those who had been through a transition process were more satisfied with the adult clinic than those who had not. Nasr et al [11], from Michigan in the USA, reported that the transition programme made the change to adult care easier. Campbell [12] in Scotland was unable to obtain an adequate data set. Our study presents data that gives further insight into problems surrounding transition and their potential solutions.

The recognition of the deleterious health and developmental effects of not having a planned transition between the CF clinics in Cape Town enabled us, as part of a remedial process, to gather data which would allow us to tailor the transition to our patients' perceptions and needs. The high response rate is encouraging both from the point of view of the data it generated and also its indication of the extent to which

those using the services wished to have their voices heard on this issue. The high rate may also represent a response to the perceived threat to specialized services in South Africa as the health service is restructured [13].

Adolescents showed a marked degree of reluctance to transfer. Fear of "not liking" the GSH Clinic seemed to be the dominant factor. This mirrors their parents' feeling and may be directly influenced by it. These attitudes are much more negative than those found in a similar study in sickle cell disease where fewer than half of the respondents expressed negative emotions [9]. This may also reflect the spread of attitudes amongst the CF community in Cape Town. The range and depth of concerns expressed by a majority of our respondents will need to be addressed if a transition programme is to be successful. This will require information to allay uncertainties and further exploration of possible specific concerns (e.g. the smaller staff complement at GSH, differing treatment protocols).

Adult-centred care requires adolescents to take more responsibility for decisions surrounding their care [14]. Adolescents will be unable to do this if they have not attained a degree of autonomy by the time of transfer. The achievement of independence is often delayed or incomplete in those with chronic health conditions owing, in part, to parental anxiety and inability to hand control to the adolescent. Adolescent respondents showed mixed feelings towards autonomy: on the one hand, valuing making their own decisions about treatment and, on the other, not considering speaking alone to the doctor to be of great importance. This dichotomy is probably a function of maturity as only one adult with CF rated speaking alone with the doctor as less than "extremely important". Parents' responses generally suggested the recognition of the need for independence in their children although they probably have difficulty translating this into action.

The negative emotions surrounding transfer and the need to build patient autonomy argue forcefully for a transition clinic in our setting, the offer of which received strong endorsement from all groups of respondents. It has been pointed out that the exact nature of a transition process must depend on the circumstances of the health services involved [4,7]. Respondents were presented with a single form of transition clinic as

this model is the only practical option given the scarce resources and the limited number of patients transferring to GSH each year.

A dominant purpose of the clinic, as seen by respondents, is to provide two kinds of information. Firstly respondents wanted information about the GSH Clinic. There are strong indications that the more those facing transfer know about "the other side", the easier the process will be [11]. Abdale et al [10] found that such information contributed significantly to patients' comfort with and confidence in the transfer. Given the degree of uncertainty about the GSH Clinic, such information becomes vital in promoting a smooth transition between our clinics.

Information on growing up with CF was the second area surveyed. In the questionnaire, we gave particular emphasis to this as there is evidence that knowledge in many areas (for example, reproductive issues [15]) is deficient amongst adults with CF. Adolescents in this study expressed little need for information on most subjects. Given that adults post-transfer feel that paediatric clinics give too little weight to issues such as alcohol, smoking and reproduction [10], this is surprising. These responses may not indicate their true feelings on subjects which their parents indicated should *not* be discussed at the clinic. Alternatively they may feel that paediatricians are not equipped to give them this information or, as found by Sinnema et al [16], there may be a delay in the development of sexuality in persons with CF.

In keeping with a previous finding [17], adolescents with CF showed little enthusiasm for "a great deal more information" on CF related subjects. This contrasted sharply with parental assessments of their information needs and is incongruent with the adolescents' degree of uncertainty about transfer. These differences probably reflect parental anxiety about the future of their children and the adolescents' optimism [16] or denial [18]. The fact that adolescent responders rated their health status as "good" or "excellent" supports this explanation. The GSH responders, looking back, felt that imparting this information to adolescents would be an important part of the transition. They also felt it was important that adolescents learn to make their own health decisions, an ability that presupposes insight born of knowledge.

Based on our findings, changes are being been made to our practice. Early in the child's life parents are informed of the continuum of CF care, given at different sites, through childhood, adolescence and adulthood. Children are encouraged to be active in decision making from an early age. From their midteens, adolescents are seen on their own for at least part of the consultation. Transfer will usually occur before the age of 18 years. The doctor from the GSH Clinic attends the RXH Clinic 2 to 3 times a year to share in consultations with adolescents and give families information about the adult clinic. The provision, currently under negotiation, of dedicated adolescent beds at RXH or GSH will further facilitate this transition. This study has raised awareness of transition issues amongst the CF population we serve. Additionally it provides a baseline for evaluating current and future changes in our adolescent and adult services as recommended by the Society for Adolescent Medicine position paper [6].

Although the study included all eligible adolescents and adults with CF in our services, the sample size was small and findings may not be readily generalized to other CF centres. However, the study underscores the need for CF services to assess patient and parent perceptions regarding transition, particularly where paediatric and adult CF care are located at separate sites. South Africa is poor compared to many places where CF is common, nevertheless, the issues and concerns of the increasing numbers of patients facing adulthood with CF [8] and those of their parents as examined in this study will be similar.

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Transition in cystic fibrosis: the ongoing story

Since we published our article the debate around transition has shifted. In the 1990s and 1980s the discussions were largely on the need of transition and the impediments to smooth passage between child- and adult-oriented services. While 'overview'-type articles still appear, much more is to be found on patient and caregiver perspectives i.e. the aspects we studied. Best practice is a subject of intense interest.

Interestingly these debates still largely take place in the paediatric and adolescent health journals. Mainstream medical speciality journals have hardly aired the issues. Schidlow and Feil's article[305] and Landau's editorial in *Thorax*[304] are rare exceptions. We attempted to break this mould by submitting our article to *Respiration*. We were not successful in raising the debate there and had to resort to a paediatric journal. This holds true for most transition literature. Until the idea of this new breed of adult patient is embraced by the world of internal medicine, the difficulties and issues repeatedly raised in the paediatric literature and in the clinics of tertiary hospitals will continue. Bye from Australia has attempted to do this recently, even using a exclamation mark in his title to encourage enthusiasm![309]

In the late 1990s the Europeans took transition issues to heart and at the time of writing are looking down their noses at the Americans' inability to have all adults with CF cared for by adult-oriented teams![310]

Viner, a former Australian paediatrician turned adolescent specialist, has led the way in orienting UK services to the transition ethic. In 1999 he penned a 'Current Topic' article in the *Archives of Disease in Childhood.* 'Efficient and caring transfer' is 'one of the great challenges facing paediatrics in the (then) coming century', he wrote.[311] He placed transition in health care in the context of a wider set of transitions facing adolescents, those with health issues and those without. This is now a major theme in the USA, too. Viner pointed out that much of the work had been done in North America and Australia and repeated much of Schidlow and Feil's[305] 1990 paradigm. He added hospital policies as an extra factor in the mix. His view of over 18 years as the best time to transfer to adult-oriented care is out of kilter with the Americans and what our patients thought. His adolescent-oriented context probably explains this difference. But, as he stated, there is no 'right time' and flexibility must be the order of the day. The essentials of an effective transition in his view were:

- Preparation
- Coordination
- An interested and capable adult service
- Primary care involvement.

Models include disease/system based and adolescent-oriented transition services. His experiences had been within the latter form at the Middlesex Hospital in London, UK.

Within a year of this article, the annual meeting on CF of the Royal Society of Medicine debated transition issues in CF. Viner repeated his message (almost word for word).[312] Bryon and Madge from the Great Ormond Street Children's Hospital, examining the psychological principles underlying transition, stated firmly that the young person needs the change of approach that comes with change of care givers.[313] Staying with paediatric caregivers emphasises the young person's difference from his or her peers. Complementing this view was that from the adult CF team in Manchester, UK. Webb and colleagues made the case for adult-oriented care but noted that the model depends on resources.[314] However what must happen is the adequate transfer of information from the paediatric to the adult service. This should include annual review reports, microbiology results, lung function trends, oral glucose tolerance test results, information on activities/sport. Fertility and reproduction

should *not* be left to the adult team to discuss, they believed. They found that their patients found taking responsibility for their own care was the most difficult aspect of growing up to adulthood with CF. Drugs, crime, alcohol and general deviant behaviour seem to have been common in Manchester! In a questionnaire survey they had found that patients noted a difference in the 'approach to care' between the child and adult services, bringing some empiric data to the earlier assertions of Rosen.[306]

At about the time Viner was bringing transition into the mainstream of British paediatrics, the Americans were analysing the structure and content of transition 'programs' in the USA. Blum and co-workers attempted to survey all such 'programs' in the country.[315] They succeeded in obtaining a 46% sample. This allowed a good feel of what was going on to be gained but could not be definitive. Most 'programs' were body system or condition specific (as with CF); 38% were offered generic services to adolescents regardless of which health condition they had. While all had multidisciplinary teams, few involved the families and patients in planning of the services. Not surprisingly the adolescent-oriented services were more likely to do this. The latter were less likely to contain sub-specialists. Funding for health service development was rare and most running costs were based on fee-for-service. Funding was seen as one of the main barriers to success in the 'programs'. Access to adult specialists was a significant problem, too. One third of 'programs' did not have access to adult primary care physicians, one fifth had no access to adult sub-specialists. The authors interpreted these findings in the following way:

> ....self-identified transition health care programs (sic) do not achieve the goal of collaborative, coordinated and integrative services.....barriers to attaining the goal are the limitations of the health care system itself.[314]

Within this less than satisfactory system, how were CF services doing?

In a context in which only 33 of 50 states had CF Foundation-approved adult 'programs', Boyle, Farukhi and Nosky, in a study not unlike ours, studied patient and parental views in their service at Johns Hopkins Medical Center in Baltimore, Maryland.[316] Like us, their aim was to use this information to improve their transition service. The context was of a newly established adult-oriented service. This resulted

in most 'pre-transition' patients, 52 in all, being in late adolescence and early to mid-adulthood (age range 18-63 years, median age 25,5 years). Unusually in this literature they studied the same patients and parents before and after transfer. The main areas of concern expressed by patients and parents alike were potential exposure to infection, leaving their previous physician and potential decrease in quality of care. Parents were more concerned than their children themselves were about the patients' ability of care of themselves. Concerns about the adult team and facilities did not feature prominently. Most concerns had been allayed by the time of the second part of the survey, but concerns regarding infection remained. A factor that particularly decreased concerns (decreases of about 1,4 in a 5 point scale and statistically significant) was having met the adult team or a member of it prior to transfer. Having spent more than three years with the paediatric team increased the level of concern. Having telephone access to a nurse once the transfer had been effected was seen as very important by the respondents (4,9 [SD 0,6] on a 5-point scale). The patient respondents expected education on adult CF issues to be important parts of the adult programme. Their parents were more specific, citing fertility and transplant expertise as important aspects expected of adult care. The whole process was seen in a positive light (4,5 SD 0,3).

Comparison of this study with ours demonstrates the influence circumstances of individual services can have on patient and parent perceptions. We studied existing services sited in separate hospitals with little contact between them. Our adult service was an established service. We studied younger patients who would transfer at a younger age. A nurse coordinator was part of neither team. We found major concerns regarding moving to the adult service; Boyle and colleagues found little.[316] Only the differential view of the young person's ability to cope between patient and parent coincided. This specificity of circumstances bedevils transition research, yet points to the need for locally-appropriate solutions. The value of the adult team being introduced before transfer is a potentially useful finding of the Johns Hopkins Hospital study. It has been seen as part of our solution to the problems highlighted in our study. A review of attitudes in Cape Town following the introduction of a transition plan would be helpful in strengthening the view that this is helpful part of achieving successful transition.

Another single centre American study of patient attitudes came from Boston. Zack and colleagues, in a service without a transition programme, explored their Children's Hospital patients' sources of health care, receipt of preventive counselling (anticipatory guidance) and attitude to such counselling.[317] As with Boyle and colleagues' study,[316] patients were mostly adults (median age 25,5 years, range 16-43). Unfortunately the sample size was only 32 despite there having been 180 potential subjects. As this was a prospective sample, study power rather than bias would be the main effect of this shortcoming. Fewer than half of the interviewees recalled preventative health care discussions. Patients felt that the ages of 13 to 16 years represented the best time for them to start seeing the doctor alone. The findings of our study (that young people were not interested in seeing the doctor alone) are referenced as a contrasting experience on this point. Of perspectives on growing older with CF only half of the patients noted 'increased independence' Most responses to this 'transition' area related to comfort with current health care providers and their expertise with CF. Perhaps reflecting this, two thirds of this largely adult population had not considered transferring to an adult-oriented service.

The findings in this centre contrast somewhat with those at the Baltimore centre. Is this because the adult centre in Boston was on another site? Did the paediatric experts have a role in producing this 'conservative' attitude amongst their older patients? Indeed adult pulmonologists were being drafted into this paediatric site to continue care for adults with CF. An eyebrow or two would be raised across the Atlantic at what was happening in Boston Children's Hospital. Did it represent a prominent strand in the care of older patients with CF in the USA?

The question of how CF services were approaching transition issues overall in the USA was investigated in a comprehensive set of studies undertaken by Flume and colleagues at the beginning of the new century, first appearing in abstract form associated with the 2000 North American CF Conference and then in a number of related papers (in the paediatric literature!).[318-20]

There were 110 CFF-approved CF centres in the USA. In the first study 104 (67% of the total) programme directors were surveyed.[318] In the second, 1288 adult patients were contacted of whom a quarter replied.[319] The third study used the internet to

survey team members apart from directors.[320] Two hundred and ninety responses, nearly half of them from nurses, were received. Perhaps the most revealing aspect of these surveys was how out of step paediatric programme directors were with the perceptions of patients and their adult-oriented colleagues. They tended to want their patients to transfer (if at all) at ages up to and beyond 21 years citing lack of 'maturity' being a reason for 'holding on to these patients. Adult patients and adult-oriented directors did not see it this way; patients wanted to be seen as mature and capable. Boyle's study from Baltimore[316] also gave this view from patients. Team members felt that transfer by 21 years was to be encouraged. Adult patients claim to have had far fewer concerns about transfer than the paediatric directors attributed to them. Team members also perceived patient concerns as only 'mild' to 'moderate'. The idea of transfer tended to be introduced to patients and families in mid to late teens, with many not meeting the adult team till the time of transfer. The quasi-parental attitude of paediatricians needs to be challenged; it is likely to be acting as an impediment to successful development and transfer of mature young CF patients.

The other significant finding was the large gap in adult services in the USA. Almost two in five (38,9%) of paediatric CF services had no associated adult service (either within their service or independent of it). A quarter of adult respondents who received centre care obtained it from paediatric centres. The authors comment that CFF directives aim to develop adult-oriented services in all centres. In a guest editorial associated with the 2004 paper, Conway from the adult CF service in Leeds in the UK opines that

> ...without exception, all patients in the center (sic) (should) move on to an established adult unit.[310]

In this way, transition is established as an expected norm in CF care. He thus found it 'scarcely credible' that so many adult American CF patients continued to receive care in the paediatric setting. The studies of Flume's group receive his commendation as their description of the current situation allows redress and points the way to improving transition through addressing attitudes and skills.

The new century has seen transition in general being encapsulated in three major policy documents. The American Academy of Pediatrics together with the Academies of Primary Health and Internal Medicine put out a Consensus statement in

December 2002 in association with a special supplement to *Pediatrics* on the subject.[321] This was one of the outputs of a special Consensus Conference on the subject held in 2001 and, through its involvement of representatives of adult services, demonstrated a new commitment to improving transition services. The 1993 statement in *Pediatrics* only involved the Pediatric Academy. In essence, the new statement said, the goal of transition in health care is

> ...to maximize lifelong functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted as the individual moves form adolescence to adulthood.[321]

Specifically the statement proposes the following six things:

- That each young person has a health care professional who attends to the issues of transition
- Make training in transition services part of certification of primary care residents and physicians' training
- Maintain an up-to-date medical summary
- Create a written transition plan by the time the child is aged 14 years
- Include general guidelines for primary care and preventive health care in the care of young persons with 'special health care needs' (the official American phrase for long term health conditions such as CF)
- Appropriate health insurance[321]

The Society for Adolescent Medicine put out a second Position Paper on transition in 2003 in the *Journal of Adolescent Health*.[322] It also followed the Consensus Conference and reiterated the six "critical first steps" to ensuring successful transition. The Society added the need for all stakeholders to take responsibility for coordinating health care, continuing education of stakeholders, adults to receive appropriate *primary* care, further steps to improve adult health care, the continuing need to develop models of 'best practice', the elimination of restrictions by health centres and funders, and further research.

In the UK in 2003, the Royal College of Paediatrics and Child Health in association with a number of other expert bodies put out a document entitled "Bridging the Gaps: Health Care for Adolescents".[323] Coming from a tradition of strong primary care, the UK experts confined transition to 'Secondary Care'. It was felt that the onus was on specialist services to adapt themselves to promote good transition practice. The role of Primary Care services in the care of young persons in transition was unexpectedly considered to be in the future, 'as the overall services are developed' (p28). Unlike the Americans, the UK document states that full transfer to adult-oriented care should not occur until the young person has 'finished growth and puberty' (p40), perhaps reflecting the views of Viner, a major role player in the production of this document. He had expressed this view in his earlier annotation in *Archives of Diseases in Childhood.*[311]

Transition services in Cape Town in the light of these recent trends

Here in Cape Town a very good relationship has developed between the paediatric and adult CF services since the need for a transition service and the associated orientation of professionals was recognised and a response planned and implemented. In parallel the Cape Cystic Fibrosis Association has also put a lot of effort into raising adolescent issues among their membership. Their administrator often attends the adult clinic and has encouraged one gregarious female adult to welcome younger neophytes to the GSH service. On the RCCH side we arrange days on which families and patients can meet Prof. Paul Willcox and we can discuss these young persons with him. This may be more than a year before transfer takes place. Teenagers are transferred in 'batches' at around 17 years of age to help them feel more 'at home' in the new surroundings. Whether this 'model', which has grown only partly by design, is fulfilling the aims of transition as voiced in recent statements remains to be seen. It contains the elements for success as suggested by the studies reviewed above: belief by both CF teams that transition to adult oriented care is appropriate; preparation from the time of diagnosis; more detailed preparation in the years immediately preceding transfer; introduction of the adult physician to family and patient before transfer, a familiar face on the adult side. Involvement of youth themselves has occurred indirectly through the Cystic Fibrosis Association and, for a short while, adolescent group work conducted by our social worker, Ms Margie Gibbons.

From the beginning of 1996 when our study of transition began to September 2003 when this cohort was completed, 16 young persons with CF have been transferred to GSH. The average age at transfer was 17,8 years (range 10 – 19 years).

As this review of the literature shows, any claim to success needs to be measured. The year 2006 will be 10 years on from the data gathering phase of our study. It behoves us to measure the effects of the changes wrought to our services aimed at improving transition for young people with CF in the Western Cape province and producing a healthier, happier, more independent adult.

END-OF-LIFE CARE IN CF

Death is rarely a sudden event in CF. There is a need for end-of-life care to be anticipated and prepared for by the health care team. This is less simple than it seems. Most deaths in CF relate to respiratory failure. However, the progressive decline of lung function is not linear. When FEV_1 measurements reach below 30% of expected correlation between lung function and the onset of the terminal phase of the disease is very difficult to determine. Patients can deteriorate clinically and then, with treatment for a pulmonary exacerbation, rally and return to baseline. Disease severity can appear to plateau; the patient adjusts to his or her disability and maintains a seemingly good quality of life. Sometimes lung deterioration can occur very rapidly with one bad exacerbation precipitating the patient into the terminal phase, unanticipated. For these reasons, deciding at which point "end-of-life" care begins is often very difficult. Yet not to make adjustments to therapies and choices would be to deny a patient appropriate quality of life in the final phases of the disease. Thus it may be more helpful to think of the terminal phase as a process rather than a point; a gradual adjustment of the goals of each element of the therapeutic regime.

As pointed out in an article by Robinson and colleagues, the terminal phase of CF may contain elements of preventative, therapeutic and palliative care.[53] For example vitamin therapy aims to prevent complications of malabsorption may never be stopped; antibiotics may be used to reduce the burden of infection in the lungs; opiates or hypnotics may be prescribed for dyspnoea or insomnia. Antibiotics were

found to have been used right up to a few hours before death in many cases in this study.

This article is one of very few on the subject of end-of-life care in CF. This being the case and, because I was struck by the very different experience of some aspects of end-of-life care they described in the USA compared with what I had been part of at the RCCH, I decided to contribute to the literature on the subject with the following letter:[54] As before, references are given at the end of the letter.

TERMINAL CARE IN CYSTIC FIBROSIS: HOSPITAL OR HOME?

Pediatrics 1998;102:436

As a member of a pediatric CF care team, I was struck by the contrast between my experience of the end-of-life care of those with CF and that of Robinson et al[1]. Whereas all but one of their child and adult patients died in hospital, in the last 10 years only 43.8% (9/21) of our patients (ages 5-21 years) have died there. In Cape Town, death has tended to occur in hospital for those living far from our center where home-based care is more difficult to administer (N=2), those with rapid deterioration (N=6) and where care in hospital has been chosen (sometimes not in so many words) by the child/young person and family (N=1). The small number choosing in-hospital care may result from differing parental or staff attitudes to dying or from differing physical facilities in the children's hospitals in Boston and Cape Town. The potential availability of lung transplantation in conjunction with an older patient group will account for some of this difference. In highlighting the complex mixture of preventive, therapeutic and palliative care that occurs in the late stages of CF, Robinson et al. draw a contrast with the end-of-life care in cancer patients. As they point out, time of death in CF can be unpredictable. However, we need to note that home care for those with cancer can have positive effects[2]. In balancing therapy and palliation in CF, it is vital for us to gain insight into patient and family perspectives beyond those hinted at in the article[3]. Are our practises meeting the needs of patients and families facing the final phases of CF? Are some of those in ICU on BiPAP, for example, not among that "proportion of patients" who "die deprived of the final comforts of actively managed terminal care"?[4] The contrasts I have drawn attention to

adjure us to ensure as scientifically as possible that, in our different settings, in the final phase of CF the broad needs of the children/young people and the families with whom we deal are being addressed.

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In the article I cited (Reference 3 above), Warner from Southampton in the UK was concerned that patients being assessed for transplantation yet rarely receiving it was denying them the choices that a realistic approach to end-of-life care can offer.[224] I was concerned to discuss this in relation to the American experience of the terminal phases of CF.

A subsequent article from Canada published in *Chest* in 2000 reported a survey of CF centres in that country.[324] Most of the 45 patients who had died in 1995, the year under survey, died as adults. Notably 77,8% of these died in hospital, and again the prospect of transplantation was a factor. Many were assessed but few were actually transplanted. Three quarters of the patients received some form of end-of-life medication. Only 35% of patients had had end-of-life care discussed more than one month before death. This being the case it is not surprising and is somewhat reassuring that

> The physicians ..... indicated a desire for assistance in providing palliative care.[324]

Despite my assertion that home end-of-life care should be considered, my experience in this province has been of many impediments to this. Support services are not readily available. In only three cases was successful hospice-supported care achieved, all three in Somerset West. In a number of cases when home care was chosen by the family, I felt support was far from ideal. The hospital team was constrained in its ability to visit homes; few services were available to entrain for patients who had received most of their care from the hospital. General practitioners assisted in two cases. Many hospital deaths were because the family could not cope at home even though they wished for an expected death to occur there. With about four deaths occurring a year in patients who come from diverse areas it is difficult to set up services to adequately deal with the complex end-of-life needs of young persons with CF. The addition of a nurse to the team could significantly help in this area.[325] How complex end-of-life needs are is illustrated in the following case study with which this chapter will end:

The Story of N

N was 16 when the point came to discuss the change in focus of his CF care. Always a quiet and uncomplaining child and now a young man of similar character, he was cyanosed but was not troubled by dyspnoea at rest. His parents who lived with him in a village out of Cape Town had a long discussion with the CF doctor. "Quality time" was now the name of the game. N, in his quiet way asked no questions, made no fuss. Home oxygen was arranged via a concentrator; the local hospital was informed of his condition. We spoke to the Medical Superintendent of his local hospital to facilitate access to any care he might need. The Reach for a Dream Foundation supplied him with woodworking tools and over the next four year (yes, four years) during admissions for pulmonary exacerbations and unpleasant back pain caused by osteoporosis (he was always sent home as soon as he was comfortable) and when he visited the CF Clinic, he would bring little products of his workbench. During one of his admissions (about two years after the talk) his parents wanted to discuss lung transplantation again. After discussion of this with them and N, the impossibility of this was accepted. Once he

arrived nearly dead because his oxygen transport cylinder ran out in the car in a mad dash to hospital. But N continued to live. Despite contact with the local GP and hospital, N's parents always wanted him to come to the Red Cross Hospital. Progressively his shortness of breath increased. He went in to right heart failure. He developed diabetes. And one day (yet gradually) his oxygen dependence and dyspnoea were such that further palliation and symptom relief would be needed. N though quiet and very much in love with his dog who always slept on his bed at home, made it clear that he did not wish to return home. Morphine was started; he found that his nebulised bronchodilators made him shaky and anxious - staff needed a lot of persuasion not to administer them. The Social worker and CF and ward doctors spent time with him encouraging him to call the shots of his care. His psychic turmoil increased. He talked as he'd never talked before. He seemed to have so much to resolve. I found that my poor command of Afrikaans let him down at times. He was frightened of death yet wanted release. He didn't want his parents to suffer. I told him that it was only the oxygen that was keeping him alive. We wanted him to be released from the strain of breathing but morphine administration and attempts to reduce the oxygen flow rate did not give release. He lived on. Then one day, knowing that his parents were on the way from home, while alone, not half an hour after the last discussion with one of us, he pulled off the oxygen quite deliberately and in five minutes was dead. N, the quiet, undemanding adolescent had chosen his moment of death as he saw best for himself and his family. His parents, although devastated by his death that they had known was imminent for four years, were quick to see the magnanimity of his act.

CHAPTER 9

PROGNOSTIC ASPECTS

OUTLINE OF CHAPTER

This chapter presents a South African perspective on survival in CF. A review of local literature is followed by my study of the subject in the Western Cape CF population, published in 1999. The chapter ends with updated figures on survival covering 29 years and an associated discussion of international comparisons and the role of socio-economic and other factors in CF survival in this region.

INTRODUCTION

Cystic fibrosis is a lethal disease. Few persons with the disease live a normal life span, even in the 21st century. In 50 years CF has gone from being a condition associated almost uniformly with death in infancy to one in which a majority of sufferers reach adulthood and in which a reasonable quality of life may be expected for many years. A major contributor to this improvement has been advances in health care. This chapter explores whether persons with CF in the Western Cape province have benefited from these improvements and what factors influence longevity in this population. In CF overall survival is, in large part, a proxy for the quality of health services: how have South African health services been doing over the last three decades?

The first study of longevity in a South African CF population was that of Hill and colleagues.[33] In this study, survival was part of a general description of CF as seen in Cape Town. The prognosis data were limited to average length of survival. Mean survival is a very crude and misleading statistic in the study of longevity. Survival times are not normally distributed and no account is taken of the age of those who are

alive at the time of the study. In CF, mean survival would have given a particularly misleading figure as those still alive would be likely to survive much longer than those born early in the study period, owing to the advances made in treatment between the 1960s and the 1980s. No statistical method can completely overcome the difficulty in measuring survival (which, as Corey in Toronto pointed out, is a moving target[326]) but Life Table or Kaplan-Meier product limit survival analysis give much better approximations. The latter method is the one I employed when studying the prognosis of CF in the 1990s. This chapter reproduces, unchanged, the report of this study as it was published in the *Journal of Paediatrics and Child Health* in 1996.[52]

Nine years have passed since the period studied in that report ended. The second part of this chapter presents updated survival curves covering 29 years of follow up of this CF population. Factors that might have influenced survival are also explored further in this section.

Study 9.1

THE PROGNOSIS OF CYSTIC FIBROSIS IN THE WESTERN CAPE REGION OF SOUTH AFRICA

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ABSTRACT

Objective: To study the prognosis of cystic fibrosis (CF) in South Africa.

Methods: Retrospective chart review of 102 children with CF over 20 years.

Results: Survival at 18 years was 54% (95% confidence intervals 30-79). Prognosis was not influenced by gender or genotype but survival was noted to be worse for

Cape Coloured children than for European children. This appeared mainly to be due to the death of 8 Cape Coloured infants, 4 of whom presented with oedema and anaemia, mimicking kwashiorkor. Infection with *Pseudomonas aeruginosa* occurred earlier in Cape Coloured children than European children (Median 1 vs 4 years) and they had a worse 5-year survival (56% vs 89% $p<0.05$) after infection. Of the 40 children born in the second decade studied, 6 Coloured and no European children died.

Conclusions: Ethnic differences in prognosis exist and are probably relate to underrecognition of CF and socio-economic status.

Key words: Cystic fibrosis; prognosis

Cystic Fibrosis (CF) is one of the commoner life-threatening genetic diseases in people of European descent and in South Africa also occurs people of mixed ancestry (a heterogeneous group of Malay/Hottentot/European/Khoi ancestry known as Cape Coloured)[1]. Since the identification of CF as an entity in the 1930s the average survival of people with the disease has risen rapidly. In the United States of America the Cystic Fibrosis Foundation reports a change in median survival from 14 years in 1969 to 28 years in 1990[2]. This increase has been ascribed to advances in management, specifically pancreatic enzyme replacement, attention to nutrition, physiotherapy and new antibiotics for *Pseudomonas*. The influence of better ascertainment of mild cases on these figures is uncertain. Projected median survival for those born since 1990 is 40 years in the United Kingdom[3]. In contrast in Latin America over the last 15 years half of the children with CF died within 7 years of the diagnosis being made[4].

In 1988 Hill *et al.*, in a report outlining the clinical and epidemiological features of CF in Cape Town, noted that 21% of 106 patients had died with a mean age at death of 4,7 years.[1] The present study aimed to explore the prognosis of CF further and to examine the factors which influence the survival of those with CF in the Western Cape region, the capital of which is Cape Town, of South Africa.

METHODS

All cases of CF (confirmed with 2 sweat tests) born in the 20 year period between the beginning of October 1974 and the end of September 1994 and who were seen regularly at the Cystic Fibrosis Clinic at the Red Cross War Memorial Children's Hospital were included in the study. Any patient who had been admitted and died, the diagnosis having been made shortly before death or *post mortem*, were (sic) also included.

For each child demographic details were recorded. The date of death or the date of last contact with the clinic was recorded with data on children who were referred elsewhere or who had been lost to follow up being censored at the date of last contact. Cause of death was ascertained from the clinical record. Variables examined were gender, ethnic group (European or Coloured, which in the present study was made up of Cape Coloured children, one Xhosa child and three Asian children), deltaF508 (DF508) status and age (in completed years) at first colonisation of respiratory secretions (nasolaryngeal aspirates in infants; expectorated sputum in older children) with *Pseudomonas aeruginosa.*

Data was captured and analysed, with the exception of survival curves, using Epi-info Version 6 (Centers for Disease Control, USA). Survival curves were generated using Kaplan-Meier product limit methods and significance levels were calculated using logrank statistics (Statgraphics Version 6.1, Manugistics Inc., 1992). For those who had been colonised with *P. aeruginosa* 5- and 10-year survival rates after colonisation were calculated.

RESULTS

One hundred and two children (52 male) fulfilled the study criteria. Twenty six children had died, of whom 18 had died in the first decade of life. All deaths after the first year of life were due to CF lung disease. Cumulative survival for the whole cohort is shown in Fig. 1. There was no statistically significant difference in prognosis between males and females (p = 0.4; Fig. 2a).

There was a significant difference in the mortality rates of European and Coloured children (10/57 vs 16/45, Chi-square = 4,25, p = 0,04 Mantel-Haenszel). Cumulative survival analysed by ethnic group is shown in Fig. 2b. Nine infants died; all except one were Coloured and their clinical histories are shown in Table 1. If infant deaths are excluded, the ethnic difference in prognosis fails to reach statistical significance (p = 0,22).

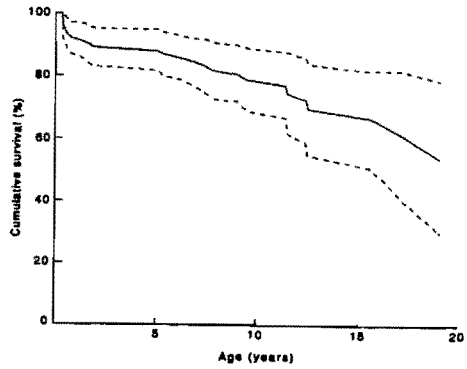

Fig. 1 Survival curve from birth for the whole cystic fibrosis population. (---) Represents 95% confidence intervals

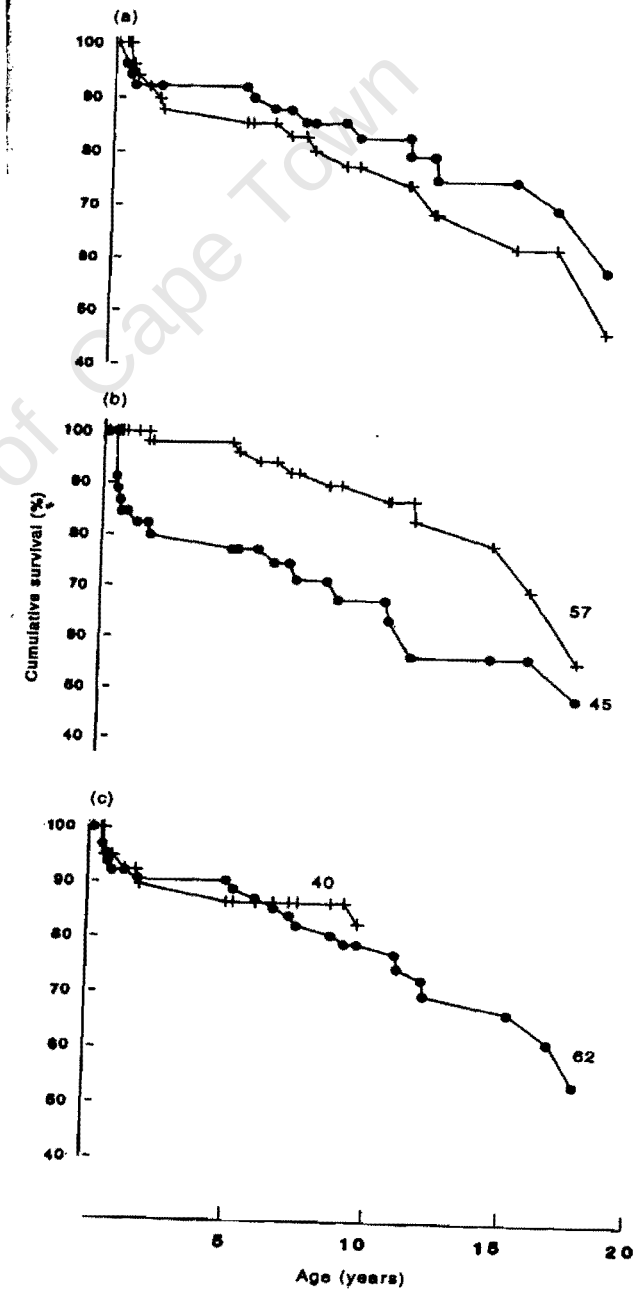

Fig. 2 Survival curves from birth. (a) Gender. (+) female, (—●—) male. (b) Ethnic group. (+) European, (—●—) Cape Coloured. Numbers indicate the size of each group. (c) Decade of birth. (—●—) 1975–84, (+) 1985–94. Numbers indicate those born in each decade.

TABLE 1 INFANT DEATHS

	Age at diagnosis (mths)	Ethnic group	Presentation	Age at death (mths)	Cause of death
1.	Birth	C	Meconium ileus	3	Pneumonia
2.	3	C	Anaemia/oedema	3	Aspiration pneumonia*
3.	3	C	Anaemia/oedema	3	Pseudomonas pneumonia#
4.	3	C	FTT/pneumonia	3	Pneumonia
5.	4	C	Pneumonia	4	Pneumonia#
6.	4	C	Anaemia/oedema	5	Septicaemia*
7.	6	C	Anaemia/oedema	6	Pneumonia#
8.	3	C	Severe pneumonia	7	Pseudomonas pneumonia
9.	Birth	E	Meconium ileus	9	Marasmus/pneumonia

* Siblings

\# Diagnosis made *post mortem*

FTT = Failure to thrive, C = Coloured, E = European

The DF508 status was known for 82 of the 102 children; 12 children died and 6 were transferred before genotyping became available and 2 had had testing deferred. Genotype did not influence mortality (Table 2).

Data for *P. aeruginosa* colonisation could not be ascertained for 5 children. The ages at colonisation for European children and Coloured children differed (Kruskal-Wallis H = 11,3, p = 0,0008). The medians were 4 years and 1 year, respectively. Survival in those colonised with *P. aeruginosa* was worse for Coloured children than for European children (56% vs 89%) 5 years after colonisation. This difference was not evident at 10 years (Table 3).

TABLE 2 GENOTYPE, ETHNIC GROUP AND MORTALITY

	Genotype (no. of deaths)		
	DF508/DF508	DF508/Other	Other/Other
European	34 (4)	9 (1)	1 (0)
Coloured	7 (3)	21 (4)	9 (2)
Total	42 (7)	30 (5)	10 (2)

N = 82.

TABLE 3 SURVIVAL, PSEUDOMONAS COLONISATION AND ETHNIC GROUP

	5 year survival*			10 year survival		
	European	**Coloured**	**Total**	**European**	**Coloured**	**Total**
Alive	17	9	26	3	4	7
Dead	2	7	9	8	10	18

* p = <0.05 (Fisher exact)

To test whether advances in survival recorded in other countries were reflected in this cohort, it was split by decade of birth. There was no change in prognosis in the first 10 years of life for the whole group (Figure 2c) but all six children born in the second decade who died were Coloured. Three died in infancy (Patients 2, 3 and 6 in Table 1) and the other 3 died at 15, 22 and 61 months of age, respectively.

DISCUSSION

Cystic fibrosis occurs in 1 per 2000 European births and 1 per 12000 Coloured births in South Africa[1]. Specialised CF Clinics exist in a number of centres. In Cape Town the Cystic Fibrosis Clinic at the Red Cross War Memorial Children's Hospital, non-racial from its inception, was set up in 1972. Until 1989, when an adult facility was started at Groote Schuur Hospital, it was the only specialised CF Clinic in the Western Cape region. It is reasonably certain that all the individuals born in this region since 1974 in whom CF has been diagnosed have been followed up at the Clinic. Cases diagnosed *post mortem* at peripheral hospitals may have been missed although the genetic implications of the disease make it unlikely that these cases would not have come to the attention of the Clinic. There may be under-recognition of CF in rural Coloured people[1].

The present study, the first to assess prognosis in a South African CF population, although limited by the relatively small number of cases, does allow some conclusions to be drawn. There is a cumulative survival of 54% at 18 years meaning that, as in other countries, provision of services for an increasing number of adults with CF will be necessary. Survival proportions for the first 10 years of life in children born between 1974 and 1985 were lower than those for the United Kingdom reported by Dodge et al[5] with 77,5% versus over 80% surviving to 10 years of age.

Infant deaths appear to be playing a significant role in the mortality rate of CF in South Africa. While for the European group the impact was minimal, in the Coloured group 50% of deaths occurred in infancy. One factor responsible for this appears to be the underrecognition of the anaemia-oedema presentation of CF. All babies with this presentation except one (in whom the anaemia was extensively investigated before the diagnosis was recognised) were diagnosed as having kwashiorkor, which is a much more common problem in the Western Cape region. Poor prognosis is often a feature of the anaemia-oedema presentation[6] but delayed and inadequate treatment would have reduced the chance of survival. Three of the nine infants who died had the diagnosis made *post mortem*. It had not been suspected *ante mortem*. This lends credence to Hill *et al.*'s contention that there is underrecognition of CF in the Coloured population[1].

Although there was a trend, in line with other reports, for females to die earlier, this did not reach statistical significance. There are significant differences in genotype between the European and Coloured populations[7] but, owing to small numbers, it was not possible to show whether this influences prognosis. Testing for the DF508 and other mutations began in 1990. With time any influence genotype has on prognosis in this population may become apparent.

No difference in cumulative survival was found between the two ethnic groups after infancy. The three post-infancy deaths that occurred in the Coloured group in the second decade studied, without any in the European group, might be ascribed to chance but in all three cases there were social and educational factors which disrupted effective management from a central clinic. Ethnic group as a risk factor probably exerted its effect through its socio-economic implications although this effect is not demonstrated for children who survive the early years. Britton[8] showed that lower social class independently worsened the prognosis of CF in England and Wales. Diminished access to and use of specialist CF clinics may result in the benefit of such centres not being felt by those who are socio-economically deprived.

First identification of *P. aeruginosa* in respiratory secretions occurred earlier in the Coloured group. This may be due to these children being more ill and therefore

having respiratory secretions cultured more frequently. Alternatively, sick children may be exposed to nosocomial infection with *P. aeruginosa* at CF clinics or in hospital wards. This group of patients is economically worse off than their European peers. Overcrowding and inadequate housing lead to greater exposure to respiratory pathogens. The poorer outcome for this group at 5 years may, in part, be due to earlier colonisation with *P. aeruginosa*. Given that mucoid strains of *P. aeruginosa* are associated with a worse prognosis[9] it would be important to ascertain the nature of the isolates. This information was not available for samples obtained in the earlier part of the study period. All these aspects will need to be examined in further studies.

The 20 years reviewed in the present study saw many advances in the management of CF. Most children in South Africa appear to have benefited but underrecognition of the disease in Coloured children and suboptimal management of children from deprived backgrounds need to be addressed. The study reported here has provided a basis from which to assess the impact of recent progress in the understanding and management of the disease. People with CF in South Africa deserve to benefit from such progress.

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Despite having relatively low numbers of subjects, the 1996 paper was able to show that persons born with CF and living in this region in the late 1970s and early 1980s had an approximately 50% chance of reaching their late teen years or adulthood. Having only 20 years of follow up the survival curve could not go beyond this point. However it also demonstrated that infant death in the coloured group was a serious problem (8 out of the 26 overall deaths; half of the deaths among coloured patients). Small numbers and the relatively short period of follow up prevented any conclusions being drawn on improvements in prognosis over time.

Study 6.2 has shown that nutritional status improved between 1986 and 1996. Zar and colleagues' cross sectional study of lung function indicated that it was well preserved in children with CF in the mid-1990s.[258] This is corroborated by data presented in Chapter 7. Nine years have elapsed since the period studied in the 1996 paper on prognosis. In that time the number of patient in the database has risen by nearly 80% from 102 to 181. As I wrote in the 1996 paper:

> 'The study reported here has provided a basis from which to assess the impact of recent progress in the understanding and management of the disease. People with CF in South Africa deserve to benefit from such progress'.[52]

It may now be possible to tease out trends and explore whether CF patients in the Western Cape province have indeed benefited in terms of survival from the progress that has been made in CF care in recent years.

Study 9.2

The prognosis of cystic fibrosis in the Western Cape province: a 29 year study

Objectives

To determine overall survival and the causes of death of patients with CF in the Western Cape province

To determine if there have been changes in survival between the 1970s and the 1990s

To determine if there has been progress in reducing the infant mortality due to CF

To determine the influence of ethnic group on the prognosis of CF in this region

To determine if age at diagnosis influences survival in this population

To determine if age at acquisition of *P aeruginosa* influences survival in this population

Methods

Study Population

All cases of CF, the diagnosis having been made as described in Chapter 2 and who were born in the 29 year period between the beginning of October 1974 and the end of September 2003 and who were seen regularly at the Cystic Fibrosis Clinic at the Red Cross War Memorial Children's Hospital, were included in the study. Any patient who had been admitted and died, the diagnosis having been made shortly before death or *post mortem*, was also included.

Study data

The following demographic and clinical data were obtained for each subject from the CF database described in Chapters 2, 3 and 4: gender, ethnic group (see Chapter 3 p33), whether the child lived in the Western Cape province from before the age of 2 years, *P aeruginosa* status (ever infected or never had the organism cultured from respiratory secretions). The date of death or the date of last contact with the clinic was recorded. Data on children who had left the

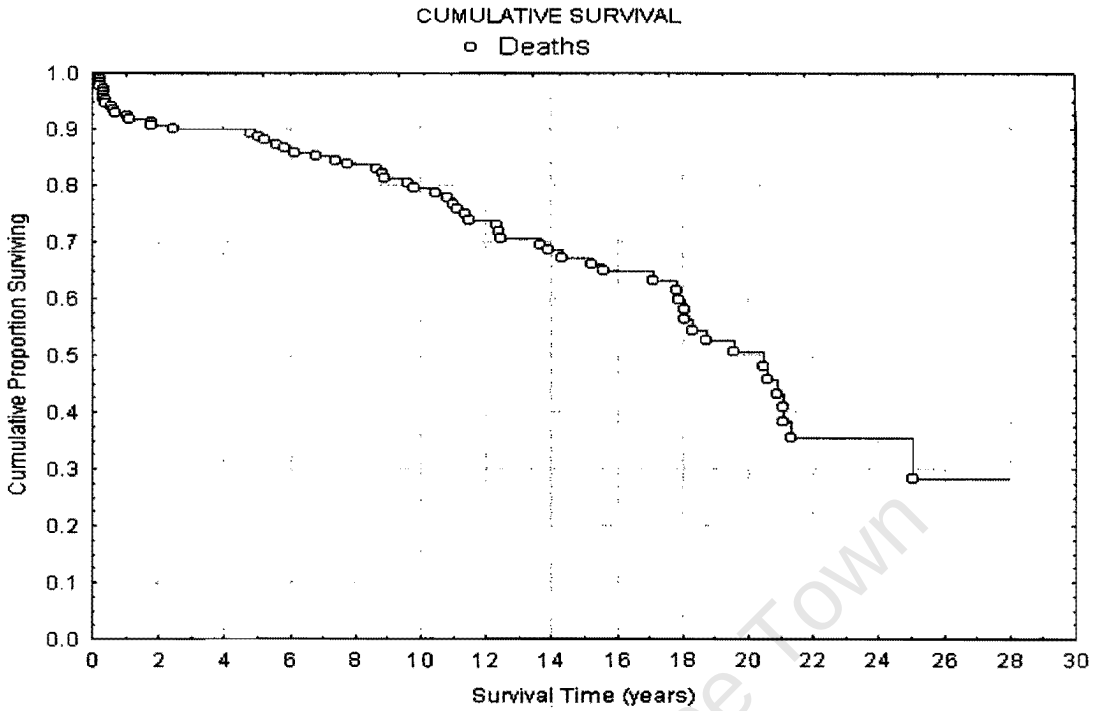
province or who had been lost to follow up were censored at the date of last contact. In an attempt to examine changes over time, the 29 year period was divided into 2 equal parts (October 1974 – March 1989 and April 1989 – September 2003). Cause of death was obtained from the clinical record.

Data was captured and analysed using the Statistica computer package (StatSoft, Inc. (2004) version 7. www.statsoft.com). Survival curves were generated using Kaplan-Meier product limit methods and significance levels were calculated using log rank statistics.

Results

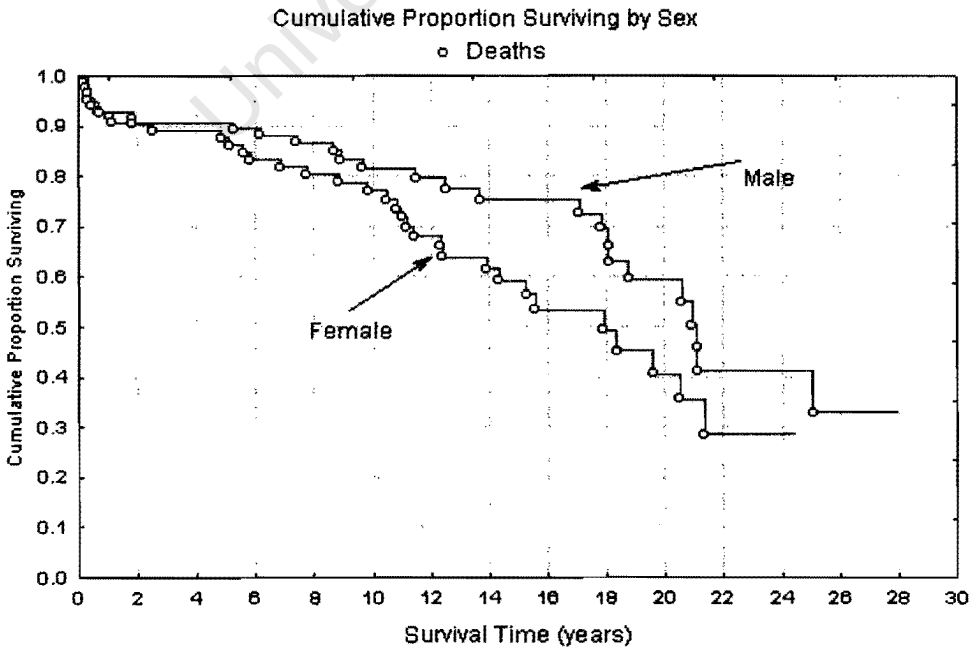
In the 29 years studied, 61 of the 181 CF patients (33,7%) had died. Mean age at death was 9,7 years. The mean for coloured patients was 7 years and 5 months and for white patients was 14 years and 4 months. Cumulative survival is shown in Figure 9.1. Median survival was 19,8 years with a 25th percentile of 11,4 years. If only those who had lived in the Western Cape province from before their second birthday were included (N = 160), the median survival was 18,1 years (25th percentile 10,6 years, 75th percentile 22,4 years).

Figure 9.1 Cumulative survival over 29 years.



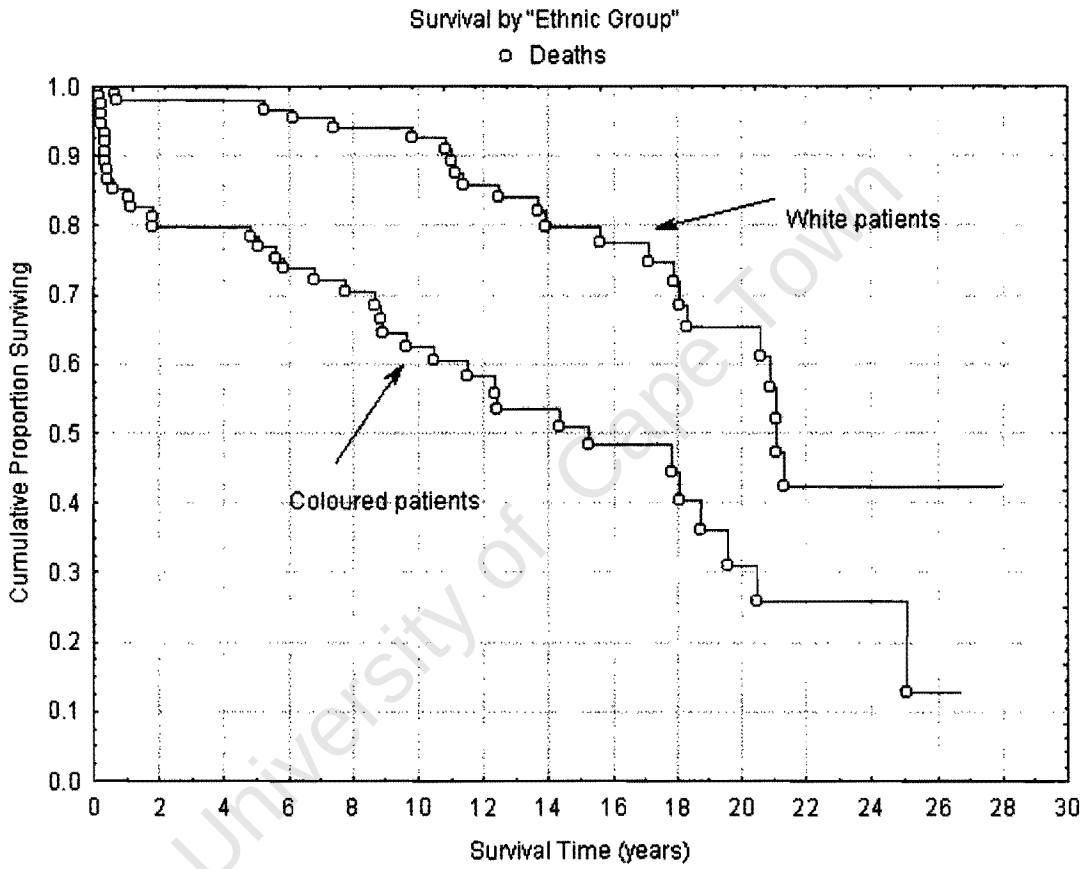
There was no significant difference in survival between males and females (p = 0,089, Figure 9.2). However if infants were excluded from the analysis (N = 162) as gender has not been shown to influence very early survival, the lesser survival of females almost reached statistical significance : p = 0.056.

Figure 9.2 Cumulative survival by sex



There was a highly significant difference in prognosis between white and coloured CF patients (p = 0,00005) (Figure 9.3). Twenty three of the 101 white patients (22,8%) had died while 37 of the 75 coloured patients (49,3%) had died (Chi^2 14,5, p = 0,00014). The median age of survival for white patients was 21 years with a 25th percentile of 17 years; the figures for coloured patients were 14,6 years and 5,6 years.

Figure 9.3 Cumulative survival by ethnic group



Of the 61 deaths all but 9 (14,8%) were due to respiratory disease. Two patients died in their teens owing to hepatic complications of CF; one teenager committed suicide; one child died at 14 months of a Reye-like syndrome; one infant died of an unexplained colitis. One infant died of sepsis associated with the anaemia/oedema complex. He had undergone extensive investigation for anaemia and died soon after the diagnosis of CF was made (see Table 9.1). One other infant had congenital hydrocephalus with severe neurological sequelae. He died of marasmus soon after the additional diagnosis of CF was made (see Table 9.1).

There were 13 deaths in infancy (21% of all deaths). Infant deaths accounted for 2/23 deaths in white patients versus 11/37 deaths in coloured patients (p = 0,1). There have been 4 infant deaths since those reported in Study 9.1, Table 1. Table 9.1 shows all 13 infant deaths. Seven infants died in the first study period and 6 in the second.

TABLE 9.1 INFANT DEATHS

	Age at diagnosis (months)	Ethnic group	Presentation of death	Year of death (months)	Age at death	Cause of death
1.	Birth	C	Meconium ileus	1981	3	Pneumonia
2.	3	C	Anaemia/oedema	1993	3	Aspiration pneumonia*
3.	3	C	Anaemia/oedema	1981	3	PA pneumonia#
4.	3	C	FTT/pneumonia	1983	3	Pneumonia
5.	4	C	Pneumonia	1981	4	Pneumonia#
6.	3	C	FTT/pneumonia	2001	4	Pneumonia
7.	3	C	FTT/pneumonia	2000	4	Pneumonia
8.	4	C	Anaemia/oedema	1988	5	Septicaemia*
9.	4	C	Hydrocephalus/FTT	1995	5	Marasmus
10.	6	C	Anaemia/oedema	1992	6	Pneumonia#
11..	3	C	Severe pneumonia	1981	7	PA pneumonia
12	4	W	FTT/Chestiness	1994	8	Colitis
13.	Birth	W	Meconium ileus	1977	9	Marasmus/pneumonia

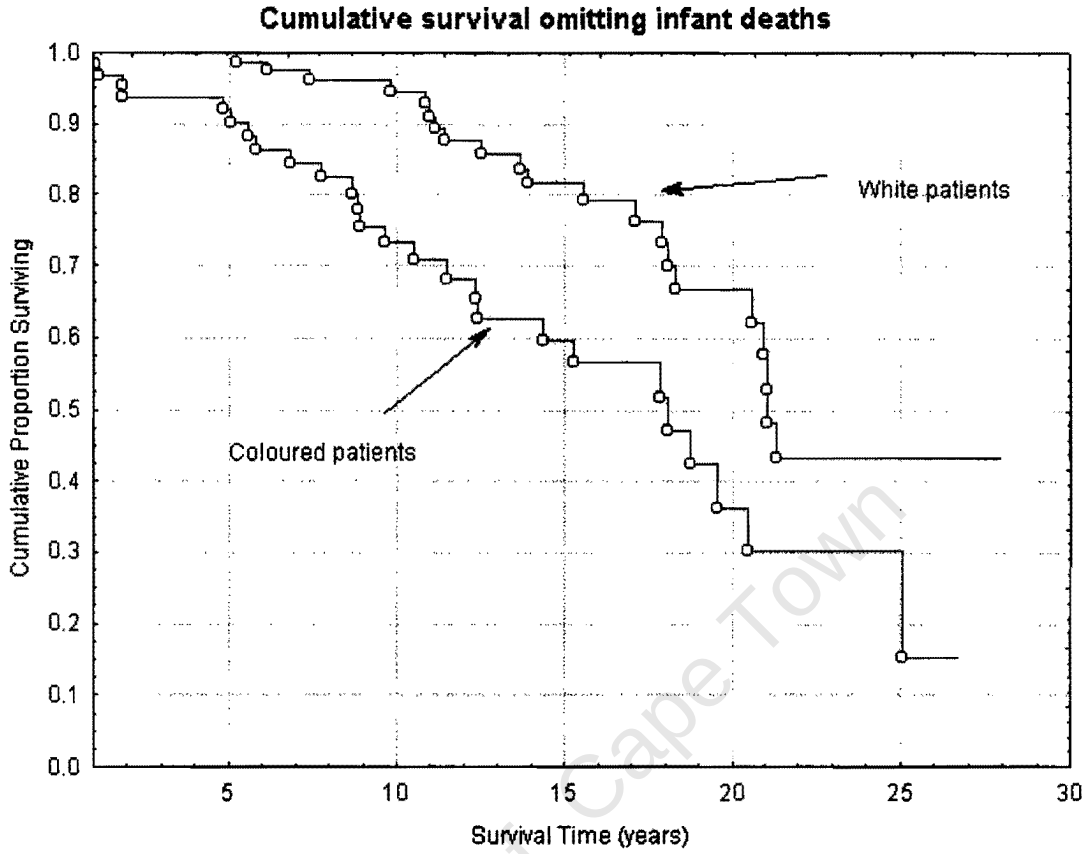
* Siblings

\# Diagnosis of cystic fibrosis made *post mortem*

FTT = Failure to thrive, C = coloured, W = white, PA = *Pseudomonas aeruginosa*

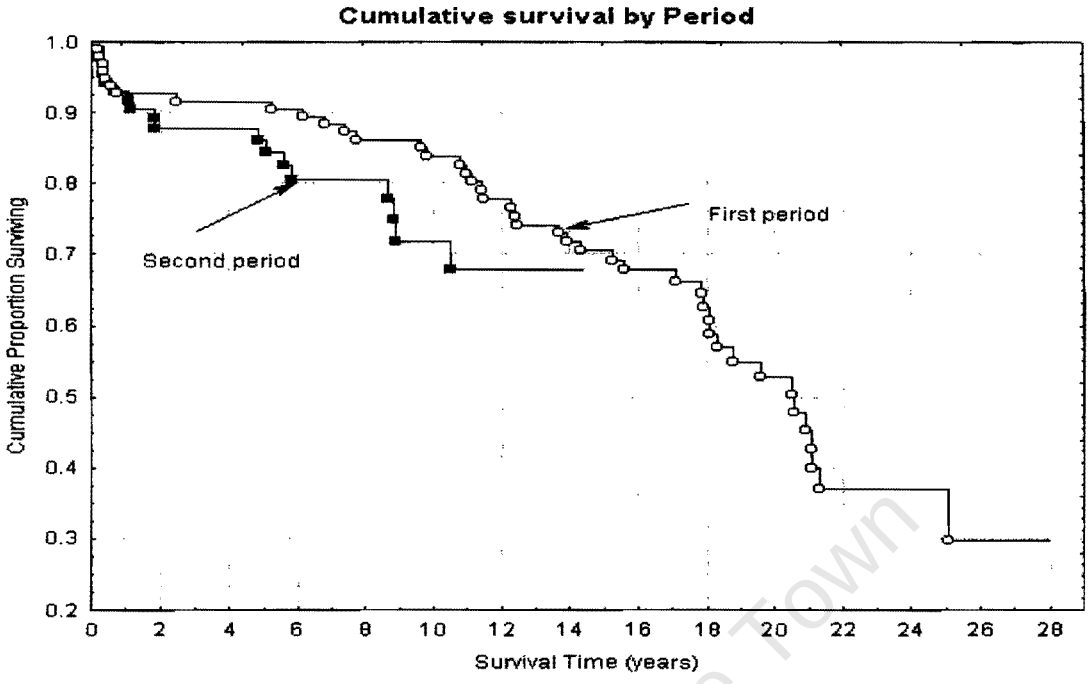
When infants were excluded from the analysis, thus excluding the infant deaths, the difference in survival between the ethnic groups remained (p = 0,003). This is shown graphically in Figure 9.4. Median survivals were 21,1 years for the 94 remaining white patients and 17,9 years for the 64 coloured patients in this analysis. This represents a 3,3 year greater median survival for coloured patients than when infants were included.

Figure 9.4 Cumulative survival by ethnic group omitting infant deaths



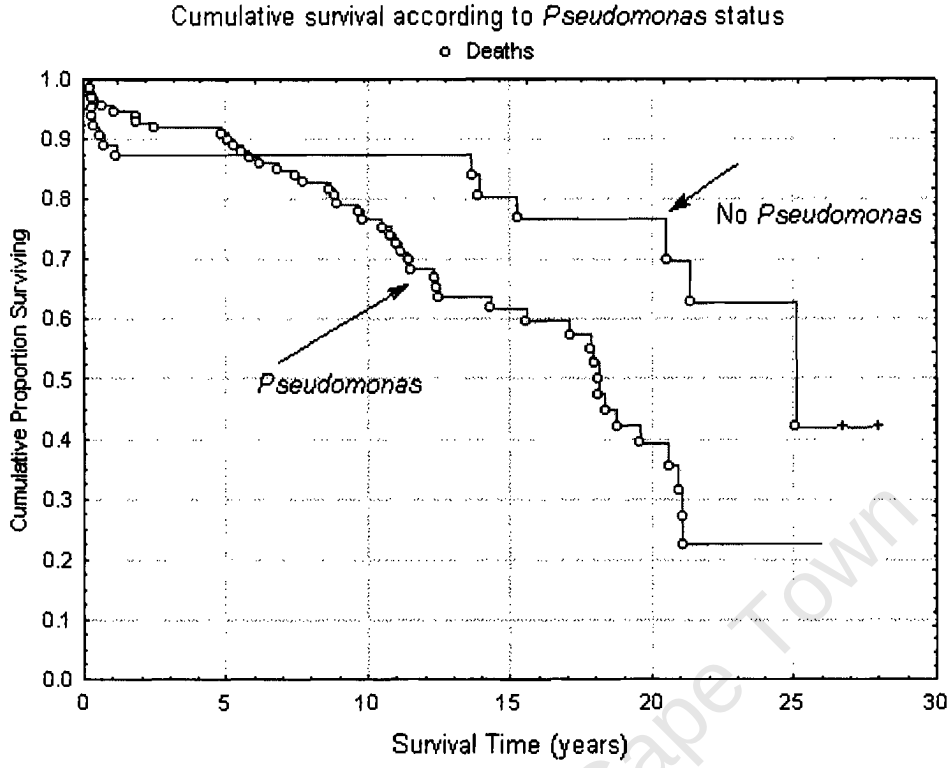
Ninety five patients were born in the first 14,5 year period and 86 in the second. In the first period 26 patients had died by 14,5 years of age; the figure for the second period was 18. There was no significant difference in survival between the two periods (p = 0,31) with survival at 14,5 years being about 70% for both periods. Figure 9.5 combines the curves for the two periods. There was also no statistical difference between the two periods for survival of coloured patients (p = 0,17). The difference in survival between coloured and white patients was significant for both periods, though only for the second period if infants were omitted from the analysis (p = 0,00035). Of the 23 deaths among white patients in the 29 years, only one was a child born in the second period. This child (the infant with colitis) was the only one of the 40 (2,5%) white children born in the second period to die compared with 17 of the 42 (40,5%) children in the coloured group (p = 0,00011). One of the four black children died. This death occurred in the first period, the diagnosis of CF only having been confirmed *post mortem* (Case 1, p67).

Figure 9.5 Cumulative survival comparing the first and second periods



The *Pseudomonas* status of three patients could not be determined. The presence of *P aeruginosa* was significantly associated with a worse prognosis (p = 0,019). Figure 9.6 shows that this deleterious effect of *P aeruginosa* colonisation was not a factor in infancy but it increased with time. Only 6 patients uninfected with *P aeruginosa* died after infancy, all of them in the second decade or beyond. In contrast *P aeruginosa* infection was associated with deaths throughout childhood and the teenage years.

Figure 9.6. Cumulative survival according to *Pseudomonas* status



Discussion

The first examination of the prognosis of CF in the population of the Western Cape province covered 20 years and involved 102 patients. In the subsequent nine years of recruitment and follow up the cohort has enlarged by over 75% to 181 patients. This is not accounted for by migration or demographic shift and therefore must arise from increased recognition of CF in the province. Although, as demonstrated in Chapter 4, this increase has not been accompanied by a demonstrable decrease in the age at which CF is being diagnosed, it must be taken as an encouraging sign. It suggests that one is moving closer to measuring the real prognosis of CF in this region, at least among coloured and white patients. The disproportionate increase in the size of the cohort also increases the chance that deeper analysis of survival and trends in this population may be possible.

Despite the 'moving target' nature of survival analysis,[326] it has the potential to influence practice and policy. For example, the demonstration that about half of those with CF born between 1974 and 1993 survived to adulthood has been used when counselling parents in the clinical setting and in motivating for appropriate adult-oriented services for CF. Similarly concerns around infant deaths and ethnic

differences in prognosis have led to reviews of clinical practice e.g. a more aggressive approach to GOR in infants with CF; greater social work involvement in the CF Service. In a decade much can change and it may have become possible to tease out further helpful information on trends.

Overall survival remains within the range identified in the first study. The attempt to measure the efficacy of CF services in the Western Cape province by excluding imported cases produced a slight but non-significant lowering of overall survival. This will largely have been due to a stronger effect of the very early deaths as no imported cases died in the first two years of life. Mean survival for the whole cohort was 9,7 years. This 'improvement' over the figure for mean survival of 4 years given by Hill and colleagues for the 1960s to 1980s[33] shows the value of a longer period of follow up. Despite this, what is new and could not be shown in the earlier study was the dramatic fall off in survival as patients entered the third decade of life. While this is partly a product of the small numbers of patients who have reached this age, the cluster of deaths at around the age of 20 years is a cause for concern. By definition these have all happened in the last decade of the study. This phenomenon represents a strong *post hoc* justification for the investigation into the circumstances of transition to adult-oriented care we undertook in the 1990s[57] and the changes we made to this process.

How does survival in this South African CF cohort compare with other countries. As an example of a developed country, comparison with the UK was made in the first study (Study 9.1) and will not be reiterated here. Survival continues to improve in such countries reaching into the 5th decade in some centres. Given the large discrepancy in *per capita* income levels and health service sophistication between SA and developed countries, such comparisons are of limited value beyond emphasising the significant influence of these 'environmental' factors on the prognosis of CF. What is the situation in other countries?

Prognosis of CF beyond the developed world

That the survival of persons with CF that has been achieved in North America, Western Europe and Australia has not been reproduced in countries that are poorer

and have less sophisticated health infrastructures is clear. Even in Eastern Europe where living standards were good compared with the developing world, survival of those with CF has not kept pace with Western countries. In fact it would appear to have lagged behind SA. CF centres only appeared in Russia in 1989. A study of 186 patients showed 41 deaths in infancy and life expectancy was thought to be about 14 years.[327]

The results presented here are a sample of what happens where CFTR mutations are less common than countries with a Western Caucasoid majority, *per capita* incomes are lower and health infrastructure is less able to meet the health needs of the population.

It is instructive to compare survival in the Western Cape province of SA with that in Latin America. There, as in SA, populations are ethnically mixed, CFTR mutations are less common than in the West and poverty is common. An initial report from Latin America suggested very poor outcomes for patients with CF: Macri and colleagues pooled information covering the period 1968 to 1989 from a number of Latin American countries in a 'preliminary communication' published in 1991.[328] In all countries survival after diagnosis (mean age at diagnosis was over 3 years) fell off rapidly, reaching from less that 20% survival at 6 years in Chile to 50% survival over the same period in Argentina. As the authors commented, these rates were 'disappointingly low'. It is difficult to compare our figures for the Western Cape province with these owing to earlier mean age at diagnosis in our region and the inclusion of 1968 to 1973, a period when the worst survival figures could have been expected, in the Latin American figures. However the South African data in Figure 9.5 for the period 1974 to 1989 (the '1st period') only reach comparable percentage cumulative survivals in the late teens, suggesting that there was better survival in SA than in Latin America in the 1970s and 1980s.

More detail from one area in Latin America, Minas Gerais state in Brazil, has subsequently been published by Reis and colleagues from Bela Horizontale. They run a CF centre that is the only centre for an area 300 miles in diameter. Bela Horizontale has a population of 3,5 million and about half of the CF patients seen at

the centre come from the metropolitan area. Four papers concerning survival in CF have come from this area.

The first, published in 1998, attempted to put a figure to cumulative survival.[329] The cohort of 111 patients, 16 (14,4%) of whom had died, had been seen between 1970 and 1994. Unfortunately the data were severely skewed by short follow up times. Only 16% of patients had been followed up for more than 6 years and half had follow up times of fewer than two years. Apparently this was not due to early deaths as survival rate was reported to be 77% at 14 years of age. Mean survival was given as 12,6 years. It must therefore have been that patients were entering the cohort well into their first decade of life and therefore represented survivors; indeed 55% of patients were diagnosed with CF after the age of 3 years. It is likely therefore that many CF patients were dying early in life undiagnosed. While this issue is not directly addressed in the paper (indeed the authors optimistically state that 'undiagnosed patients are possibly mild and moderate cases and, theoretically, have a better prognosis'), the authors do note that

> There is a lack of awareness and experience in (sic) many physicians in Brazil for suspecting and recognizing the early manifestations of this disease....[329]

These factors all contribute to questions as to the validity of the results of this study. Thus the cumulative survival given in this paper, poor as it was and despite the authors' views, is likely to have been an over-estimate of true survival in Brazil.

In a later paper using the same cohort Reis' group attempted to explore factors that predicted outcomes in their CF population.[330] The results were presented in a slightly different way. For example, follow up times were given as a mean of 8,85 years. Data from the previous paper shows that the median must be nearer to 2 years of follow up since 46,9 % of patients were followed up for fewer than 2 years. Given the caveats expressed in the preceding paragraph, it is difficult to use these data to compare with the situation in our region. The infant death data from this article are discussed below (p279). Camargos and colleagues noted that ethnic group classified, much as ours was, on skin colour did not influence outcome.[330] Ten out of 55 (18,2%) 'whites' died and 7/55 (12,7%) 'non-whites' died (p = 0,49). Proportional

hazards methodology could not tease out a difference. Relative hazard for death of being 'white' was 1,65 on univariate analysis and 1,10 (95% CI 0,40-3,01, p = 0,853) on multivariate analysis. Mean ages at death were 4,01 and 4,86 years respectively, a figure very similar to Hill and colleagues report on CF in the western Cape Province in the 1960s to 1980s.[33] In the Brazilian population, Camargos and colleagues comment, 'socioeconomic status is indirectly related to ethnic group',[330] a situation similar to SA. It is possible that with longer follow up times these difference will appear as strongly in Brazil as they have in the Western Cape province.

In their third paper the Brazilians attempted further analysis of prognostic factors in CF. Oliveira and colleagues used a later but overlapping cohort of 127 patients who had been seen between March 1977 and December 1997.[251] That this was largely a recent cohort is indicated by the fact that over three quarters of these patients (78%) were seen after 1990 and median follow up was 44 months. Again only a small proportion had died (16%) meaning that comparison with our longer and more uniform (in terms of stable patient numbers over time) study is not really valid. Length of follow up was so much shorter than that reported here that cumulative survivals are not comparable and do not indicate real outcomes in a middle income, ethnically diverse society. Thus our South African data seems to represent the best assessment yet of real survival from CF in such non-Western societies.

Despite this, in terms of prognostic factors in such a society, the study is not devoid of interest. In the light of the prognostic differences in survival with CF between socioeconomic/ethnic groups in SA, Oliveira and colleagues' observations regarding nutritional status are interesting. Birth weight seems to have had prognostic significance with weights below 3000g having a survival probability of 59% (95%CI 41-77) versus 87% (95%CI 77-97) for birth weights 3000g and above.[251] The relative risk of birth weight below 3000g was 5,95 (95%CI 1,7-15). Low birth weight is common is SA's coloured population.[331] Could this not be influencing outcomes from CF in this group? Other nutritional factors such as wasting and low height for age also carried a worse prognosis but this is not unique to Brazil or Cape Town (see below and Chapter 6). In Brazil the presence of *P aeruginosa* was also associated

with worse prognosis in univariate analysis (though not in multivariate analysis), but again this is not unique to poorer countries. At variance with modern CF experience in developed countries was an association between early diagnosis (specifically diagnosis before 3 months of age) and poor outcome. This is likely to have been in part due to MI. In the fourth paper, using the same 127 patients, the same authors showed that the 9 patients with MI had lesser survival than those without MI.[332] In a society where poverty plays a role in the rapid progression of CF-related disease owing to poor nutrition, hygiene and environment, the youngest children are likely to be most vulnerable to these adverse circumstances. This Brazilian data has resonance in the population we have studied: except for MI and siblings, early diagnosis was associated with early severe disease, and increased likelihood of very early death. Later diagnosis means that for genetic or other reasons the children were less symptomatic. To study this in more depth using proportional hazards methodology could be informative in SA.

Trends in survival

Once again change in survival over time was not found (or was not demonstrable). The shapes of the two curves in Figure 9.5 are very similar. Infant deaths wiped out 10% of patients in both periods and just under 70% of patients were alive at 14,5 years. It is to be hoped that later survival of the second cohort will exceed that of the first. This has already occurred for the white group with only one death occurring and that an unusual one in infancy.

This widening gap between the two main 'ethnic' groups requires further examination. This second study has been able to demonstrate what was suspected at the time of the first study: coloured patients do not survive as long as white ones. The phenomenon exists in the present more than it did in the first half of the study period. This represents the most important challenge to the health service and the CF Service. What factors are leading to this difference? The large number of infant deaths will be dealt with separately (see p278). As this study shows, deaths among coloured patients exceeded those among white patients for the whole study period. My experience would suggest that rather than biological factors, social factors were leading to this differential survival.

The role of social factors: socio-economic status, ethnicity

In the first study reported in this chapter I noted the likely role of social factors in the early deaths of coloured children with CF. Now that overall mortality and not only early mortality has been shown to be worse in the coloured CF population the role of social factors deserves further scrutiny. No formal assessment of social factors has been undertaken in this population in recent years. In her study of the CF knowledge of persons with CF and their families in Cape Town in the 1980s, Henley took parental occupation as a proxy for social class.[38] Of sixty families, 45% were in social classes I and II. The ethnic make up of these social class groups was not given. Henley found that parents from lower occupational classes had greater need for information about CF than those in the higher groups and seemed to have received less such information.[39]

As discussed in Chapter 3, the exact influence of ethnic group on CF phenotype and survival has been difficult to tease out. The CFF registry study of 601 African American CF subjects[111] suggested that most differences (including worse nutritional status) were not likely to be of biological origin, but rather were mediated through socio-economic status. Another registry-based study published in 2001 was unable to identify African-American 'race' as an independent risk factor for worse pulmonary function[333] (see p275). Non-Caucasoid populations outside of the USA have been small making it difficult to dissect out differences. Bowler and colleagues in Leeds in the UK studied nine Asian patients each of whom was age- and sex-matched with two white patients.[334] They noted a number of differences that may have had prognostic significance (e.g. earlier acquisition of *P aeruginosa*, lower respiratory function test results, lower weight for age and weight for height). Again socio-cultural or socioeconomic factors confounded any assigning of direct causality: a significant proportion of these patients attended clinics less regularly and some mothers did not speak English. Likewise in SA, although the coloured group represents one of the largest non-Caucasoid CF groups in the world, it is impossible to separate ethnic group from social factors. Apartheid specifically dictated a lower socio-economic level for coloured people and high rates of deprivation are found in many communities. Although as discussed in Chapter 3 coloured patients in the Western

Cape province are genetically distinct, their poorer prognosis of CF cannot be attributed to their ethnicity.

Indicators of lower socio-economic status have been shown to influence morbidity from and survival in CF in other settings. In the UK, Britton published a paper in 1989 in which he attempted to study the effect of social class on CF survival.[335] His study appears to have been stimulated by a report from the Brompton Hospital in London that showed a disproportionate attendance at the CF clinic of patients from higher social classes.[336] Was differential access to such centres of expertise discriminating against poorer patients and thus adversely influencing their survival (and overestimating the value of such centres)? Using death certification data that included a measure of social class (parental occupation), his data suggested .that social class associated with manual labour independently led to an age at death above the median when compared with non-manual employment. The odds ratio for death for males was 1.47 (95%CI 1,16-1,87) and for females was 2,75 (95%CI 2,16-3,52). Britton himself recognised that the presence of CF in a family may influence social class itself through choices the mother (e.g. foregoing a highly paid career) or adult CF patient (e.g. unable to undertake manual labour) has to make, but felt that this was unlikely to have confounded the validity of his conclusions. He also showed that, with the increase in survival from CF from the 1960s to the 1980s, these differences appeared to be growing. Subsequent letters in response to this paper suggested that the reason for the Brompton Hospital's higher social class clientele related to a tendency for higher class patients to gravitate to London and did not in itself negate the positive effects of centres of expertise.[337] While the premise for Britton's study may have been less valid, his results are not. Even in the UK, lower social class was influencing survival among persons with CF. How this detrimental effect was mediated was not studied. Reduced access to specialised expertise for poorer families, as suggested by Britton, may be one factor. This aspect has been studied in three papers from the USA.

Curtis and colleagues published the first study on socio-economic factors in CF in 1997.[338] They studied both socio-economic status (SES) and health insurance in a cohort of 189 CF patients who had been born between 1959 and 1970 in the North

Eastern USA. SES was measured using parental occupation. Health insurance compared no insurance, Medicaid (which is offered to poor families in the USA) and private insurance. Factors controlled for were those known to influence prognosis adversely: female sex and presentation with MI. Age at diagnosis was also controlled for, although whether it adversely affects prognosis equally in all situations is not clear. Health insurance as an independent risk factor was assessed by controlling for SES. Year of birth was entered into the analysis to check for a cohort effect given the long time of recruitment and follow up. None was found. Patients without health insurance were twice as likely to die as those on Medicaid or with private insurance. In the USA, not to have insurance is associated with being in the gap between eligibility for Medicaid and being able to obtain private insurance through one's employer. This equates to low income status but also is likely to deter patients from accessing health care even in the centre under study, a CFF-sponsored centre 'accepting referrals independent of ability to pay'.[338] This supports Britton's contention[335] but adds the idea that access to *any* form of health service a CF patient might require may be affected by low income. In the study, lower SES was also associated with worse survival. The authors note that this situation is not unique to CF, though the examples they cite (breast cancer, AIDS, cardiovascular disease) have aetiologies that include factors related to SES. CF being a single gene disease is therefore different; social factors exert their influence on severity only after the onset of the disease (*pace* birth weight, see p270).

A second paper was published in the same edition of *The Journal of Pediatrics* as the registry-based study of CF among African Americans by Hamosh and colleagues,[111] cited above in the discussion of ethnicity. This juxtaposition was noted in an editorial by Harris from Cincinnati.[339] He took the differences noted in the care of poor and African American CF patients very seriously, noting that they were not unique to CF. They suggested that 'medicine.. [was]..failing in some very significant ways.[339] This applies just as much to health services in the Western Cape province of SA, despite the efforts to improve the situation that were presented in Chapter 8. Every effort must be made to compensate for the health effects of poverty. However it must be asked whether health services can ever completely compensate for socio-economic deprivation and cultural factors. In the paper Harris was referring to, Schechter and

colleagues from North Carolina in the USA studied CF in those on Medicaid (a proxy for SES) compared with those who did not use it and found reduced lung function in the Medicaid group.[340] This group was also more likely to be African American.

Later Schechter and colleagues took this further and studied survival in CF in more detail using a much larger cohort – the CFF Patient Registry. They published their paper in 2001 using data on 20 390 CF patients below the age of 20 years between 1986 and 1994.[333] Again health insurance status ('Always on Medicaid' versus 'Never on Medicaid') was used as a proxy for SES. Added socio-economic factors were rural residence and 'race'. The large number of patients allowed the influence of SES on outcomes other than survival to be assessed. Health service utilisation (controlled for pulmonary function status) was one of these. Regarding survival, those 'always on Medicaid' did poorly compared with the 'never on Medicaid' group. Over the age of 5 years, the relative risk for the first group was 2,02 compared with the second. Contrary to the 1997 USA study,[336] the 'no insurance' group did no worse in terms of survival than those 'fully insured'. However there was no 'never insured' group so comparison of the two studies is difficult.

When controlling for a number of potential confounding variables, analysis showed that pulmonary function was worse in the Medicaid group, as had been shown in Schechter and colleagues' first study.[340] The Medicaid group also had lower weights and heights. They were more likely to be below the 5th percentiles for weight (odds ratio 2,31) and height (odds ratio 2,22). Medicaid patients had more admissions for pulmonary exacerbations than non-Medicaid patients (odds ratio 2,38). This persisted even when their worse pulmonary function status was controlled for. Ambulatory visits to speciality care (about four visits per year) did not differ between the groups. Thus in this, the largest study ever undertaken of SES in CF, SES produces significant relative worsening of biological indicators that predict survival.

The role of biological factors in survival

As discussed above, non-biological factors such as income levels and health services provide the most likely and strongest explanations for lower life expectancy for CF in SA relative to Western countries. The large numbers of CF patients seen in the

developed world has enabled studies of biological factors that influence survival in CF to be studied. Could any of these factors be exerting a strong influence here?

Hudson and Phelan presented some of the first work on survival factors in CF. They studied 622 patients in Victoria, Australia, looking at the effect of age at diagnosis, sex and mode of presentation on survival.[341] Their work which covered the years 1953 to 1981 was published in 1987. If deaths under 6 months were excluded , the main risk factors at that time were a 'predominantly respiratory' presentation and MI. The lack of improvement in lung disease soon after diagnosis led to worse lung function later in life compared to those in whom it improved. As shown in Chapter 4, beyond a higher incidence of the anaemia-oedema complex, there was nothing exceptional in the way CF manifests itself in SA; specifically, respiratory presentation were not unusually common. Thus these factors are unlikely to have contributed significantly to the relatively poor outlook for CF patients in the Western Cape province.

A number of studies have shown that nutritional status at diagnosis and beyond influences prognosis. In older CF subjects wasting has been shown to be an independent predictor of survival. Sharma and colleagues in London, UK demonstrated that patients who were less than 85% predicted ideal weight had a worse 5-year survival than those above this level.[342] This was independent of lung function. As shown in Chapter 6, low weight for height, a measure of wasting, was found in one third of SA CF subjects, the proportion increasing with age. Two studies have shown relatively short stature to influence survival in CF. This measure was part of a prognostic model developed by those studying transplantation in CF, again in London. Height was entered as a continuous variable in this study. Together with lung function, white blood cell count and the presence of liver disease, it accurately predicted 1 year survival in an older population of CF subjects (median age 20,17 years).[343] A study from Washington DC in the USA that used 19 000 CF subjects in the years 1980 to 1989 from the CFF Patient Registry investigated the role of stature in the survival of children who had reached the age of 7 years.[344] Height below the 5th percentile gave a relative hazard of dying after the age of 5 years of 2,9 in males and 4,3 in females. The risk increased for children who had short stature at 7

years of age. While the authors of this paper do not give the proportion of children who were stunted at these ages they quote the 1988 CFF Patient Registry data: a stunting rate of 23% for all patients. The figure we reported from Cape Town for 1996 was 16,2%,[55] but this figure omitted the patients with the worst lung disease. Weight for age *z*-score has also been implicated as a survival factor. Liou and colleagues, also using the CFF Patient Registry, found it to be part of 5 year survivorship model not unlike the one produced in London using stature.[345] The studies presented in Chapter 6 illustrate that while improvements were taking place in the Western Cape province, the nutritional status of young CF patients in the 1980s and 1990s left much to be desired. In SA this factor is difficult to disentangle from socio-economic and health service influences. As suggested in Chapter 6, a simple health service intervention such as regular height measurement may have improved average nutritional status and therefore survival. So, despite the well demonstrated influence of nutritional status on survival in Western countries,[16 346] whether it is independently responsible for poorer median outcomes in SA is questionable. It must be noted that, whether independent or not, nutritional factors are particularly likely to have exerted their malign influence on the coloured CF patients. Further study using proportional hazards methodology might be helpful.

Lung function, particularly FEV_1, has been used in predictive models for survival in CF.[347] This has usually been in the context of optimising the timing of lung transplantation in older subjects, which is not relevant to a birth cohort such as this. It is also not an independent factor, being dependent of other factors such as nutritional status and *P aeruginosa* infection. *P aeruginosa* infection itself has been shown to be associated with earlier mortality by Henry and colleagues in Australia.[265] Its deleterious effect on lung function, the final common pathway to death for most patients with CF, has been outlined in Chapter 7. Rates of infection in SA were not higher than those seen elsewhere. If it has been a factor in the relatively early demise of CF patients in this region its effect may have been through reduced access to appropriate treatment, another socio-economic effect.

Other factors that have been found to influence survival in CF are CFRD[348] and infection with *B cepacia*.[347] Neither of these complications was common enough to have influenced overall survival in this cohort.

Infant deaths

The large number of deaths in infancy in this cohort deserves special attention. In developed countries infant death from CF is now rare. The survival curves generated for this population for the years 1974 to 2003 show a remarkable parallel with those from Victoria, Australia from 1955 to 1980 as reported by Hudson and Phelan.[341] Both have many deaths in infancy and a median survival of 18 to 20 years. The causes and trend in early deaths are different. MI accounted for most of the Australian infant deaths and almost disappeared as a cause of death in the 1970s, while in Cape Town MI-related deaths were few and deaths in infancy continued at an unchanged rate to the present. In Victoria the number of deaths under 6 months of age in the 10 years 1955 to 1965 was 65; only 10 children died by that age in the subsequent 15 years to 1980. Hudson and Phelan give MI as the cause of 5 of these latter deaths i.e. half; respiratory causes numbered 3 and the cause of death was unknown in the other two cases.

In Sweden, a European example, a similar reduction in infant mortality from CF has been achieved.[349] Survival curves generated in a survey of all patients with CF in the country between 1961 and 1999 showed a significant infant mortality in the 1970s but almost none from the 1980s onwards. Causes of death in infancy were not given in the paper. Analysis of the USA's CFF Register by Kulich and colleagues in 2003 showed very few infant deaths in the decades reviewed here e.g. 4/1000 CF births in 1985 and 10/1000 CF births in 1999.[350] Again causes of infant death are not given. Britton, studying the effect of social class on CF mortality through death certification, tabulated a change from 106 infant deaths in England and Wales in 1959 to 4 in 1986.[335] Dodge and colleagues' study of the incidence, population and survival related to CF in the UK showed a progressive reduction of infant deaths from 90 in 1974 to 1976 to 11 in 1992 to 1994.[351] These 11 infant deaths were out of an estimated 949 CF births in those three years, or a cause specific infant mortality rate of 11 per 1000 CF births. The equivalent figure for the Western Cape province in the

1990s was 62,5 per 1000 CF births (3/64). An analysis of the role of CF screening in reducing infant deaths from CF was undertaken in Wales in the 1980s. In a study of the cause of deaths before the age of 5 years, five infant deaths occurred in a five year period during which 176 children with CF were born.[352] Causes of death were cot death (1), respiratory failure (2), MI and chest disease (1) and prematurity with MI (1). Interestingly 3 of the 5 infants were not from the screened group but were diagnosed before the screened group. The most recent data from the UK suggests that since 1994 one infant death due to CF occurs every three years.[353]

As discussed above, CF prognosis is poorer in non-Western countries. Infant deaths as found in Cape Town are likely to contribute to this. In Arab countries infant mortality from CF is reported to be high. For example, in Jordan, Rawashdeh and Manal reported that 38 of 202 children with CF died, 'most of them below 1 year of age'.[354] Following other authors from Arab countries, the authors ascribe this to severe mutations and consanguinity. They also noted another 110 deaths, mostly at less than 6 months of age, in extended families with high levels of consanguinity that probably were due to CF. Other factors called on to explain these early deaths were

> Poor physiotherapy, lack of nutritional support and the limited supply of enteric-coated pancreatic enzymes...[353]

suggesting major deficiencies in health services for CF.

The study from Brazil by Camargos and colleagues reported 5 infant deaths out of the 111 CF patients seen at a referral centre in the years 1970 to 1994.[330] This was 29,4% of the 17 deaths which is not unlike the 21,3% (13/61) of the deaths in the Western Cape province over much the same decades. As noted above, very early deaths from CF may be being missed in Brazil but the persisting urban/rural difference in incidence in CF for coloured patients in the Western Cape province (see Chapter 3) suggests that the same phenomenon exists in SA. MI was not implicated in the Brazilian deaths but no further details were given preventing further comparison.

The first study reported in this chapter brought the extent of the contribution of deaths in infancy to the mortality of CF in our region to our attention. Improved post-operative care and the T-tube procedure were already bringing down morbidities and

mortalities in infants with MI when the study report was published. In the 1990s we had recognised the contribution of uncontrolled gastro-oesophageal reflux (GOR) to the rapid progression of lung disease in some infants and had adopted a more aggressive approach to investigation and treatment of this association. In the light of this, the four subsequent infant deaths and two deaths in the second year of life deserve further scrutiny.

As Table 9.1 shows, two patients died of unusual conditions: hydrocephalus (not known to be associated with CF) and a severe enterocolitis. Details of the latter case are sketchy as the child died in a private hospital. According to his paediatrician he had a rapid onset of severe abdominal distension associated with bloody diarrhoea and died on a ventilator. This could have been due to intussusception, a complication of CF, but could also have been due to an unrelated infection. Pseudomembranous colitis is less likely as he had not been on antibiotics at the time. Case 163 (Appendix A) who died at 14 months had a Reye-like syndrome with lethal cerebral oedema, not a known association with CF.

The remaining three patients all had rapidly evolving lung disease. Case 141 had his early care at TBH and required prolonged ventilation for severe chest disease early in infancy. On transfer at the age of 11 months he had severe obstructive lung disease and carried a methicillin resistant *S aureus*. This combined with a home in a poor rural Karoo town proved lethal within two months of transfer.

The other two infants, both born in the new century had remarkably similar courses. They presented with severe pneumonia with peripheral airways obstruction and failure to thrive at three months of age. Neither left hospital alive despite relatively rapid recognition of the underlying CF, nasojejunal feeding, airway clearance and vigorous antibiotic therapy under the care of the CF service's pulmonologist. In the light of current norms in Western countries, cases such as these remain a challenge to the CF service. Is it a factor intrinsic to the children's genetics (all three were coloured infants) or is there something missing in our therapeutic regime? Regarding CF genetics, all three of these children had one copy of the ΔF508 mutation and two had a copy of the 3120+1G A mutation i.e. CF mutations were not unlike many of

the other children. Studies of immunological allotypes in coloured children in the Western Cape province have identified that their genotypes differ from white children.[355] It is possible that a key gene that regulates the immunological response in the presence of CFTR mutations has a differing form and therefore effect in some coloured CF children who do particularly badly, even with modern CF care. Such interactions are being recognised as contributing to the variability of the phenotype/genotype relationship in CF. With regard to clinical care, the full range of antibiotics, laboratory and other testing, monitoring and nutritional care is available at the RCCH. Only screening is likely to have such children diagnosed earlier than they were and this is not practical for these children given the relative rarity of CF in SA and the cost of mutation analysis. Careful attention to clinical features and the effects of each aspect of management in future children may give clues to factors (e.g. low birth weight) that have been leading to such poor outcomes.

The role of gender

Female gender has been associated with a worse prognosis in CF particularly after the first decades of life. Factors suggested to explain this phenomenon have included higher resting energy expenditure,[356] gender roles[357] and body image.[358] As discussed above (p92) there is marginal later diagnosis of CF in females in the USA. Whether there is earlier infection with *P aeruginosa* is not proven (p282). In both studies reported in this chapter no gender factor could be demonstrated using survival analysis though there is a trend for worse survival among females (Figure 9.2). As shown in Chapter 4, females were diagnosed earlier than males in this province. This may have represented worse early symptoms in females, the predominance of late diagnoses in males or may have been a product of chance. The survival curves were widest apart during the teenage years (Figure 9.2), reflecting one's personal experience of females doing worse at this age but this cannot be demonstrated statistically.

Future survival in the Western Cape province

What can be expected in the next 10 years? In the concluding paragraph of the first study (Study 9.1) I stated that '(P)eople with CF in South Africa deserve to benefit from such progress.' (i.e. recent progress in the understanding and management of the

disease). It seems as if most white patients have been. They have been benefiting from new PERT formulations, new antibiotics and new ways of using them (e.g. early eradication of *P aeruginosa*, long term inhaled aminoglycosides or colistin), support and knowledge from participation in peer groups such as the Cystic Fibrosis Association and the excellent comprehensive services offered at the RCCH. Rural residence has been no object to this group. Despite problems in SA's public health system on which most CF patients depend, middle class children with CF can expect to enter adulthood, probably with good lung function. It may be difficult to distinguish some of these children and adolescents from the European counterparts. Simultaneously for others, despite the availability of the medications and services described above, the risk of death in infancy or rapid deterioration is likely to remain as strong as it did in the 1980s and 1990s, unless new ways are found of overcoming the malign effects of poverty and deprivation. This challenge must be taken up at local, regional and national level for all poor children with long term health conditions. Since my statement in the 1996 paper[52] few of the (potentially expensive) breakthroughs in management of CF that were promised at the time (e.g. gene transfer therapy, new pharmacological agents to stimulate CFTR) have come about. A quantum leap forward in this area might not be affordable in SA. This would lead to an increase in the differential survival between developed and resource poor nations. In the mean time SA health services and CF services particularly must continue to strive to deliver optimal standard care, at least that set out in the SA Consensus Document on CF in SA,[359] to all CF patients.

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APPENDIX A
Study population

Key: YEAR = Year of diagnosis
SEX: M = male; F = female
ETHNIC: C = coloured; W = white; B = black; A = Asian
NA: sweat sodium in mmol/l
CL: sweat chloride in mmol/l
Genotype: CFTR allele1 / CFTR allele2; ? = no mutation found after testing for SA mutations; blank = no testing or only tested for DF508
HISTO = diagnosis supported by histology or *post mortem* findings

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
1	1978	M	C	107	125	DF508/	
2	1975	F	W			DF508/DF508	
3	1985	M	W	92	93	DF508/DF508	
4	1975	M	W	+	+	DF508/DF508	
5	1978	F	W			DF508/DF508	
6	1976	M	W			DF508/DF508	
7	1976	M	W	100	119		
8	1982	F	C	123	129	DF508/	
9	1976	M	W	99	134		
10	1976	M	W	78	103	DF508/	
11	1978	F	W	86	101	DF508/DF508	
12	1977	F	W	91	116		
13	1983	M	C	73	80		
14	1979	M	W	107	125		
15	1977	F	W	80	135	DF508/DF508	
16	1977	M	C	75	102	DF508/DF508	
17	1980	M	W	111	117	N1303K/?	Yes
18	1980	M	C	88	82		
19	1979	M	W	125	131	DF508/	
20	1981	M	C	102	108		
21	1980	F	W	62	83	DF508/G551D	
22	1981	F	C				Yes
23	1987	M	W	117	120	DF508/DF508	
24	1982	F	W	86	150		
25	1980	F	W	83	99	DF508/DF508	
26	1980	F	C	90	105	DF508/DF508	
27	1981	M	C	80	115	DF508/3120G>A	
28	1985	F	W	121	130	DF508/DF508	

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
29	1982	M	W	105	117	DF508/	
30	1980	M	W	78	91	DF508/DF508	
31	1981	M	W	128	124		
32	1995	M	C	106	96		
33	1989	M	W	87	101	DF508/DF508	
34	1986	M	C	147	143		
35	1981	M	W	66	82		
36	1981	F	W	85	101	DF508/DF508	
37	1981	F	C				Yes
38	1981	M	C				Yes
39	1981	F	C	99	98	3272-26->G/?	
40	1981	M	C	66	86		
41	1981	F	W	56	75	DF508/DF508	
42	1982	M	W	90	103		
43	1982	M	W	159	182		
44	1986	M	W	85	118	DF508/DF508	
45	1984	F	W	84	116	DF508/DF508	
46	1983	F	C			DF508/DF508	
47	1982	F	W	+	+	DF508/	
48	1982	F	C	72	87	DF508/	
49	1993	M	W			DF508/DF508	
50	1983	F	W	102	126		
51	1983	F	W	77	89	DF508/	
52	1983	F	W		100		
53	1984	M	W	92	97		
54	1986	M	W	112	112	DF508/	
55	1987	M	W	113	126	DF508/DF508	
56	1983	F	W			DF508/DF508	
57	1983	F	C	121	138		Yes
58	1984	F	C	82	119	DF508/?	
59	1984	M	W	76	103	DF508/G551D	
60	1986	F	W	91	95	DF508/DF508	
61	1989	F	C	+	+		
62	1984	F	C	64	86	DF508/	
63	1994	M	C	110	114	DF508/?	

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
64	1990	F	W	101	101	DF508/DF508	
65	1987	M	W	99	113	DF508/DF508	
66	1986	F	C	110	125	DF508/	
67	1985	F	C	84	104	DF508/	
68	1985	F	C	84	93		
69	1985	M	W	96	109	DF508/	
70	1989	M	C	101	116	DF508/DF508	
71	1985	F	W	88	110	DF508/DF508	
72	1988	M	W	+	+		
73	1986	M	W	78	104	DF508/DF508	
74	1997	M	W	123	116	DF508/	
75	1987	F	W	94	123	DF508/DF508	
76	1986	F	W	75	106		
77	1987	F	W	67	89	DF508/DF508	
78	1987	F	W	100	121	DF508/DF508	
79	1989	M	C	86	91		
80	1993	M	C	102	108	DF508/?	
81	1988	F	W	+	+	DF508/	
82	1988	M	C	114	146	DF508/DF508	
83	1991	F	W	91	92	DF508/DF508	
84	1991	M	W	102	125	DF508/DF508	
85	1987	F	C	106	123	DF508/	
86	1996	M	W	92	97	DF508/	
87	1994	F	W	108	115	DF508/DF508	
88	1989	M	C	95	109	DF508/G542X	
89	1988	M	C	82	106	DF508/3120G>A	
90	1988	F	W	98	118	DF508/	
91	1988	F	W	70	110	DF508/DF508	
92	1988	M	C	105	110	DF508/	
93	1992	F	W			DF508/DF508	
94	1994	F	W	75	73		
95	1990	M	C	78	80	DF508/G551D	
96	1990	F	C	+	+		

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
97	1999	M	W	115	122	DF508/	
98	1989	F	W	+	+		
99	1989	F	C	81	96	DF508/DF508	
100	1990	F	C	78	102	DF508/3120+1G>A	
101	1994	M	C	71	75	DF508/	
102	1996	F	W	97	103	DF508/	
103	1991	M	C	0	0	DF508/DF508	
104	1991	F	C			DF508/DF508	
105	1994	F	W	96	108	DF508/DF508	
106	1992	F	W	0	0	DF508/DF508	
107	1993	M	W	94	97	DF508/DF508	
108	1991	F	W		135	DF508/DF508	
109	1992	M	C			DF508/	Yes
110	1999	F	W	+	+		
111	1993	M	C	92	105	3120+1G>A/3120+1G>A	
112	1994	M	C	97	104	3120+1G>A/?	
113	1992	F	C	72	104	DF508/	
114	1992	F	C	110	96		
115	1994	M	C	81	74		
116	1992	F	W	73	75	DF508/DF508	
117	1993	F	C	67	88	DF508/?	
118	1993	M	B	94	104	3120+1G>A/3196del54	
119	1996	M	W	107	126		
120	1993	M	C			DF508/	
121	2002	M	W		53	DF508/A455E	
122	1995	F	A	+	+		
123	1996	M	W	119	113	DF508/DF508	
124	1994	F	C	80	94	DF508/DF508	
125	1994	M	W			DF508/DF508	
126	1994	F	W			DF508/DF508	
127	1994	F	C	93	104	DF508/	
128	1995	M	C	62	98	DF508/DF508	
129	1995	M	W	77	101	DF508/G551D	

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
130	1996	M	W	81	93	DF508/	
131	1998	M	C	96	102	DF508/DF508	
132	1995	F	W			DF508/DF508	
133	1997	F	C	92	105	DF508/	
134	1995	M	W	68	90	DF508/DF508	
135	1995	M	C	86	88		
136	1995	M	W	+	+		
137	1995	M	W	76	84	DF508/	
138	1996	M	C	108	108	DF508/	
139	1998	F	W	72	71	DF508/A455E	
140	2003	M	C	75	67		
141	1996	M	C	+	+	DF508/3120+1G>A	
142	1996	M	C	92	105		
143	1997	M	W	99	105	DF508/	
144	1999	M	C	74	73	?/?	
145	1998	M	W			DF508/DF508	
146	1997	F	C			DF508/DF508	
147	1998	F	C	114	121	DF508/DF508	
148	1998	M	W		90	DF508/DF508	
149	1998	M	C	60	82	DF508/DF508	
150	2002	M	C	108	111		
151	1998	F	C	57	68	DF508/	
152	1998	M	C	91	94	DF508/3120+1G>A	
153	1998	M	C	97	122	DF508/?	
154	1998	F	W	81	83	DF508/394delTT	
155	1998	M	C	85	89	DF508/DF508	
156	1998	F	W	79	105	DF508/DF508	
157	2002	M	W	115	115	DF508/DF508	
158	1999	F	C	83	102	DF508/DF508	
159	2001	M	B	101	94	?/?	
160	1999	F	C	+	+	DF508/	
161	2000	M	C	80	116	3120+1G>A/G551D	
162	2001	M	W	122	120	DF508/DF508	

StudyNumber	YEAR	SEX	ETHNIC	NA	CL	Genotype	HISTO
163	1999	M	C	98	104	3120+1G>A/3120+1G>A	
164	2000	F	W			DF508/DF508	
165	2002	F	C		110	DF508/3120+1G>A	
166	2001	M	W	94	110	DF508/DF508	
167	2003	F	W	95	109	DF508/DF508	
168	2000	F	C	73	113	DF508/3120+1G>A	
169	2001	F	W	78	94	DF508/DF508	
170	2001	M	W	103	115	DF508/	
171	2001	F	C	82	109	DF508/	
172	2002	M	W	100	105	?/?	
173	2002	M	W	76	88	DF508/DF508	
174	2002	M	C	88	109	DF508/3120+1G>A	
175	2002	M	W	74	88	?/?	
176	2002	M	W			DF508/W1282X	
177	2002	M	W			DF508/DF508	
178	2003	F	B	101	97	3120+1G>A/?	
179	2003	F	W	81	112	DF508/DF508	
180	2003	M	W	100	115	DF508/DF508	
181	1986	F	B	95	133		Yes

APPENDIX B

Cystic Fibrosis Clinic Consultation Record

Date / / CYSTIC FIBROSIS CLINIC VISIT
Age y m Last Admission.....
Wt kg ↑ → ↓
Ht cm ↑ → ↓ WFH %

HISTORY

Chest .....

.....

.....

GIT .....

.....

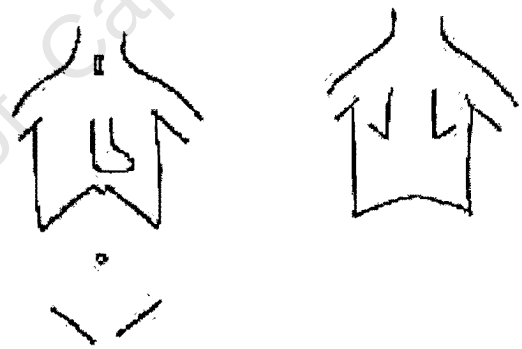
Appetite/Diet .....

Other events, admissions .....

.....

EXAMINATION

General Clubbing Y / N



CVS/Respiratory
Pulse rate /min
Resp. rate /min
Recession Y / N
Air trapping Y / N

Abdomen

ENT

Other

ASSESSMENT General .....

New Problems	Investigations	Results
1 Respiratory Y / N	Sputum Y / N	.....
2.		Antibiotic.....
3.	PFT Y / N	FVC..... FEV1 .....
	Cults	.....

Therapy *Adjustments*
1 Diet .....
2. Enzyme .....
3 Respiratory .....
4 Other .....

Consultations Dietician.....
Physiotherapist .....
Social worker.....

Special Issues Education/Behaviour/Genetic/Financial/Family/Social/Other .....

Next visit 1/12 2/12 3/12 6/12

To be done/discussed..... Signature.....